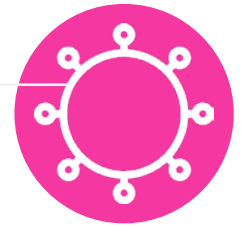


Optimising Antimicrobial Stewardship to Tackle *Clostridioides difficile* Infection and Improve Patient Outcomes



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Interview Summary

Clostridioides difficile, formerly known as *Clostridium difficile*, is a Gram-positive spore-forming and toxin-producing bacterium that causes diarrhoea in vulnerable patient groups. It is a common hospital-acquired infection but also occurs in the community. Typically, *C. difficile* colonises the gut in patients experiencing gut dysbiosis, for example, following antimicrobial treatment or chemotherapy. Cases of *C. difficile* are increasing worldwide, both in healthcare settings and in the community, and are an indicator of widespread antibiotic use. Antimicrobial stewardship (AMS) combines local, national, and international guidelines for good antimicrobial practice, effective monitoring of antimicrobial resistance, and control of antibiotic use. Such strategies are vital in the international drive to stem the rise in antimicrobial resistance and control hospital-acquired infections such as *C. difficile*. However, implementation of such strategies is often lacking. Resourcing issues and a lack of awareness of current best practices among physicians, prescribers, and the general public are significant barriers to implementation. EMJ spoke with two infectious disease experts: Benoît Guery, University Hospital of Lausanne, Switzerland, and Javier Cobo Reinoso, Hospital Universitario Ramón y Cajal, Madrid, Spain. They highlighted the challenges that face medical practitioners, infectious disease experts, hospital managers, and healthcare providers in developing and implementing effective antimicrobial strategies that support better patient outcomes. The two experts also discussed the changes required to ensure that good AMS can be implemented at local, national, and international levels.

INTRODUCTION

C. difficile is a Gram-positive spore-forming and toxin-producing bacterium. In patients with gut dysbiosis, *C. difficile* colonises the intestines and can cause debilitating diarrhoea, which may result in recurrent episodes as well as death. *C. difficile* is a common hospital-acquired infection that often affects patients receiving antibiotics, who are receiving chemotherapy, or who are immunocompromised in any way. Patients >65 years of age are at particularly high risk, and recurrent infections are common.¹ The number of cases of *C. difficile* in healthcare settings and the community is a good indicator of levels of antimicrobial use, with high levels of antibiotic use driving antimicrobial resistance.²

Worldwide, resistance to antimicrobial agents poses a major threat to human health. Recent estimates indicate that 1.27 million deaths per year can be attributed to antimicrobial-resistant bacteria, with the greatest burden in western sub-Saharan Africa.³ Two-thirds of deaths associated with infection are due to resistance to first-line antibiotics including fluoroquinolones and β -lactam antibiotics, including carbapenems, cephalosporins, and penicillins.³

Across Europe, levels of antimicrobial resistance vary between countries and can be linked to differences in the number of prescriptions written for antibiotics.⁴ The European Centre for Disease Prevention and Control (ECDC) estimates that more than 670,000 infections occur in the European Union/European Economic Area (EU/EEA) each year due to bacteria resistant to antibiotics, and 33,000 people die as a direct consequence.⁴ Despite evidence that AMS strategies can reduce resistance and hospital-acquired infections such as *C. difficile*, fewer than one-half of the countries that have approved guidelines also have strategies to implement them.⁵ In most cases, the cost is a factor. Personnel responsible for implementing and monitoring AMS in hospitals are often not funded, and in the case of *C. difficile* infections, cheaper antibiotics are commonly prescribed rather than more effective, expensive alternatives.

EMJ interviewed Guery and Cobo Reinoso, infectious disease experts working in Switzerland and Spain, respectively. This article summarises

their opinions on how good AMS programmes can help to tackle antibiotic resistance, *C. difficile* incidence, and improve patient outcomes. The experts also outline how some of the challenges facing healthcare professionals in implementing such strategies might be addressed.

WHAT IS THE SCALE OF THE PROBLEM OF ANTIMICROBIAL RESISTANCE AND HOW DOES IT VARY BETWEEN COUNTRIES?

Global levels of antimicrobial resistance are a growing threat to health. However, the burden of resistant pathogens varies significantly between countries and regions, with the highest burden in sub-Saharan Africa.³ There are many possible reasons for this, including variations in prescribing practices and the availability of different antimicrobial agents. Cobo Reinoso commented that “we tend to think of bacterial resistance as a phenomenon of Western academic hospitals. But the reality is that in low-income countries without access to recent and novel antibiotics, multidrug-resistant bacteria pose a greater burden of disease and death.” Cobo Reinoso also stated that “in low-income countries, fewer antibiotics are available. In addition, the lack of resources to make microbiological diagnoses can create the conditions for more treatment failures and late detection of resistance.” Guery added that countries with high levels of antimicrobial resistance often do not have the financial resources to implement effective AMS programmes. They also vary significantly in their policies on the delivery of antibiotics. “You have countries where you have really open access to antibiotics. In other countries, all classes of antibiotics can be prescribed by any practitioner. So, the problem is really that you cannot control the prescription by itself,” Guery explained.

NATIONAL AND INTERNATIONAL GUIDELINES ON ANTIMICROBIAL STEWARDSHIP EXIST TO HELP CONTROL INCREASING RESISTANCE BUT ARE NOT IMPLEMENTED IN MANY PLACES. WHAT ARE THE CHALLENGES, AND HOW CAN THEY BE OVERCOME?

Despite more than 70% of countries having national guidelines to support good antimicrobial practices, including policies on hand hygiene in hospitals and guidelines for antibiotic prescribing, fewer than one-half of countries have effective strategies to implement current guidelines.⁵ One of the issues, explained Cobo Reinoso, is that within healthcare settings, a range of physicians make decisions on the treatment of infections. “Infections are complications of any speciality and therefore antibiotic prescribing will be handled by different physicians within hospitals, for example, cardiac surgeons, rheumatologists, pulmonologists, and oncologists,” Cobo Reinoso explained. “We need more effective interaction between the infectious disease experts and the prescribers.”⁶

“Information is important and continuous communication and education within hospitals can help,” agreed Guery. “One of our main targets for education is young doctors. If a patient has a fever, they may prescribe a broad-spectrum antibiotic. With experience, doctors realise they can restrict antibiotic spectrum even empirically. They are more likely to wait for microbiological data on the patient that allows them to choose a narrower spectrum antibiotic.”

In 2017, a systematic review showed that effective AMS reduces both multi-resistant infections and the incidence of *C. difficile* in hospitalised patients, particularly when combined with improvements in infection control measures.⁷

Cobo Reinoso explained that “in recent years, a great effort has been made by infectious diseases units and services in Spanish hospitals to establish programmes for optimising the use of antibiotics (PROA).⁸ These programmes include regular educational interviews and peer-to-peer interventions between advisors and prescribers. Colleagues from Andalusia, Spain, have implemented an

impressive PROA in every hospital in the region, achieving very significant decreases in resistance and mortality from bacteraemia.”⁹⁻¹¹

However, there are complexities in implementing AMS programmes. “A survey in Spanish Hospitals carried out in 2019 found that although 89% of hospitals have antimicrobial strategies in place, in only 50% of cases, managers recognised that implementing the PROA was time-consuming, and only 18% of the centres had specifically recruited a professional to implement the strategy,” said Cobo Reinoso.¹² Cobo Reinoso believes that to achieve what most experts believe would constitute a truly effective AMS programme additional resources are required and AMS needs to be recognised as a top priority.¹³

In Guery’s hospital setting in Switzerland, some restrictions are in place to help control the use of antibiotics. “We have a limited group of practitioners who can prescribe certain newer broad-spectrum antibiotics depending on the patient’s condition and microbiological profile,” Guery explained.

For Cobo Reinoso, the key to good antimicrobial stewardship is having an infection expert available at short notice for informal consultancy. “An oncologist will call me because he or she needs help in managing an infection in a particular patient. Sometimes I can make a very rapid assessment and say this patient does not need antibiotics or 5 days of antibiotics is enough to treat this pneumonia.”

“It is important to remember that first and foremost, we want to achieve the best clinical outcomes for patients,” Cobo Reinoso emphasised. “Certainly, there are specific infections and nosocomial infectious complications whose prognosis is improved when infectious disease specialists directly care for or collaborate in the management of patients.”¹⁴⁻¹⁷

HOW SHOULD ANTIMICROBIAL STEWARDSHIP PROGRAMMES BE MONITORED AND GOVERNED TO ENSURE GOOD OUTCOMES?

“Like any quality programme, the AMS must be evaluated through indicators. The structure and process indicators that monitor how the AMS

team carries out its function are relatively easy to choose," said Cobo Reinoso. "However, outcome indicators are difficult. How do we measure the quality of antibiotic prescriptions? There is no perfect standard."^{18,19}

Guery emphasised that ongoing education is key and auditing the hospital's AMS programme is vital. "Ensuring that staff change their behaviour following audit results is what counts," Guery said. Indicators of efficiency are also vital, Guery continued. "Indicators of efficiency include constant monitoring of antibiotic consumption and following the evolution of resistance within the hospital. It is also very important to provide clinicians with the state of resistance of the classic microorganisms they will encounter in their daily practice."

"The evolution of local resistance is undoubtedly something that must be monitored, but it is not the sole responsibility or result of AMS policies," Cobo Reinoso commented. "In my opinion, the ideal would be to have certain indicators of the process and result of the most serious infections that would allow us to affirm that these patients receive the most appropriate care. We must also carry out prescription quality studies focused on objective parameters, such as duration of treatment," Cobo Reinoso said.

In relation to monitoring *C. difficile* infections, in Lausanne, Guery's team has been developing a scoring system to help measure outcomes for patients with *C. difficile*. "We have been developing a composite score that is associating cure and death at Day 10 with sustained clinical cure and death at Week 8. This score helped us to develop arguments to show that fidaxomicin was associated with a better outcome compared to both metronidazole and vancomycin,"²⁰ stated Guery.

WHICH ANTIMICROBIAL STEWARDSHIP STRATEGIES ARE SHOWING PROMISE IN REDUCING CASES OF CLOSTRIDIODES DIFFICILE IN HOSPITAL SETTINGS?

The duration and the number of antibiotics administered to patients increase the risk of *C. difficile* and a reduction in antibiotic use can contribute to a reduction in the number of episodes of *C. difficile* infection.^{2,21}

"Not all antibiotics confer the same risk of developing *C. difficile*.²² Therefore, patients who have recently suffered *C. difficile* and need antibiotics should be assessed by an infection expert to verify the correct indication and advise on the least harmful antibiotic," stated Cobo Reinoso.

Also, new products that maintain a healthy gut microbiome in patients treated with antibiotics are under development.²³ "If their development is successful and they can be safely administered to at-risk patients, this would be an exceptional breakthrough," Cobo Reinoso said.

"*C. difficile* infection rates can be used as a good indicator for antibiotic use," Guery said. "If you reduce the quantity of antibiotics generally in the hospital, you see a reduction in the number of *C. difficile* cases but, beyond that, you cannot be more specific."

Guery continued by stating that "in the case of *C. difficile* treatment itself, it is about good practice. It is better to use an antibiotic with a narrower spectrum, like fidaxomicin, which decreases systemic effects, rather than vancomycin or metronidazole, which are associated with increased risk of recurrence and potentially selection of resistant bacteria like vancomycin-resistant *enterococcus*."

Studies have shown that when fidaxomicin is used as a first-line antibiotic against *C. difficile*, recurrence rates and all-cause mortality rates are reduced.²⁴ Recently, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) updated the treatment guidelines for *C. difficile* infection, recognising the need to consider the risks of recurrence along with disease severity when prescribing antibiotics.²⁵ Metronidazole is no longer recommended for treatment of *C. difficile* when fidaxomicin or vancomycin are available. Fidaxomicin is recommended as the preferred agent for treatment of initial and first recurrence *C. difficile* infection, with faecal microbiota transplant or bezlotoxumab added to standard of care antibiotics for further recurrences.²⁵

FOR PATIENTS AT HIGH RISK OF CLOSTRIDIODES DIFFICILE RECURRENCE, WHAT IS THE IMPACT ON QUALITY OF LIFE AND SHOULD THIS BE CONSIDERED A PART OF DECISION-MAKING ON ANTIBIOTIC USE?

Cobo Reinoso explained that recurrent *C. difficile* infection is associated with hospital readmissions and higher mortality.²⁶⁻²⁸ In Spain, the cost of a recurrence of *C. difficile* requiring hospitalisation is estimated at 10,000 EUR.²⁹

“Recurrent infections have a big impact on patients’ quality of life. They often feel depressed and may be in isolation, cutting them off from friends and family.³⁰ We should not forget that in older patients, diarrhoea often leads to incontinence. This is terrible for the individual’s self-respect, and they worry about developing a chronic illness. It also increases their dependency on carers and relatives,” Cobo Reinoso said. “As a doctor, when you care for people with *C. difficile*, you can quickly see that these people are suffering a lot.” Cobo Reinoso added: “Unfortunately, these issues are not on ‘top of mind’ for decision makers, and I am afraid sometimes not even for physicians when deciding treatment options for their patients. We need more research addressed to study the importance of quality of life in patients with *C. difficile*.” Guery added that “there is increasing awareness of the importance of integrating patient associations into health care decisions. The ESCMID study group for *C. difficile* is currently working on a document to emphasise this issue.”

“A similar situation occurs with antibiotic resistance. Difficult-to-treat infections are associated with longer hospital stays and poorer health outcomes and, therefore, severely impact the quality of life of patients who suffer longer hospital admissions, more adverse events, and isolation in hospitals.” Cobo Reinoso added that “if we were more aware of the benefit of avoiding this problem, we would devote more resources to its prevention.”

HOW CAN A MORE COHERENT APPROACH TO CLOSTRIDIODES DIFFICILE CASE REDUCTION BE ENCOURAGED?

“Globally, if the amount of antibiotic use is huge, you will still see *C. difficile* infections, even if narrow-spectrum antibiotics are in use,” explained Guery.

“Efforts to reduce the incidence of *C. difficile* in hospitals and in the community through more appropriate and prudent use of antibiotics is everyone’s responsibility, although the AMS team must work to train other health care workers and design effective policies,” reiterated Cobo Reinoso. In addition, “it should be the responsibility of the AMS team to ensure that patients with *C. difficile* are treated appropriately and according to the latest recommendations to improve clinical outcomes for patients.”

“One thing that we could do, as was done in England, is to have mandatory reporting of *C. difficile*. This is really important because it is an indicator of antibiotic stewardship, but it is also an indicator of how you deal within your hospital with antibiotic policy. Having mandatory and systematic reporting to have good data on *C. difficile* prevalence and incidence is important,” Guery said.

Guery also pointed out that good methods for diagnosing *C. difficile* are important. A study at a reference centre in France asked 20 hospitals to send all their liquid stool samples to the reference lab for analysis. “They found that only one-third of infections were correctly diagnosed. Another one-third were false negative, the last fraction was in fact not even tested and if you don’t look for it you don’t find it,” Guery emphasised.³¹

“Several studies have shown that it is possible to improve the management of patients with *C. difficile* with simple interventions that involve carrying out an assessment and therapeutic recommendation on the cases of *C. difficile* diagnosed in an institution,”³² Cobo Reinoso said. “It is also important to consider what happens when a patient experiences a recurrence and needs access to the healthcare system. They need a reference professional who can answer them promptly.”³³

HOW CAN HEALTHCARE PROFESSIONALS BE ENCOURAGED TO MAKE DECISIONS BASED ON HEALTH ECONOMICS RATHER THAN COST AND CONSIDER THE NEEDS OF HIGH-RISK PATIENT GROUPS?

“This is a really a big issue,” stated Guery. “In hospitals today, managers ask us to provide the best treatment, but the economic perspective has increased in importance. This is a real problem in the treatment of *C. difficile*.” Guery continued: “When you consider the available molecules to treat *C. difficile*, there are some cheap ones that are not recommended anymore, such as metronidazole. Then we have another drug that is a bit more expensive and is working, vancomycin, and then we have something that is more expensive, fidaxomicin, which is better compared to the two other drugs when considering the disease as a global entity (including cure, mortality, and recurrence). If you measure the cure at Day 10 you will get rid of the disease with both the cheaper and the expensive antibiotic. But the risk of recurrence is high, and the impact on quality of life can be huge, and these should be taken into account,” Guery said. “Hospital directors cannot put a price on these things and as clinicians, it is difficult for us to convince them on the use of the high-cost drug. In our hospital we have come to an arrangement, where we prescribe fidaxomicin in patients at high risk of recurrence including those over 65 years, those on concurrent antibiotic therapy, and those who are immunosuppressed.”

Cobo Reinoso reiterated the point and said: “We have two new drugs, the antibiotic fidaxomicin and the monoclonal antibody bezlotoxumab, both have shown superiority over standard treatment with vancomycin, in avoiding recurrent infections, and both are very safe. Despite this, the doctor must justify why he is going to use fidaxomicin or bezlotoxumab. Ideally, he or she should have to justify why he or she is not going to use fidaxomicin or bezlotoxumab.”

“More independent pharmacoeconomic studies are needed to provide further evidence,” said Cobo Reinoso. “Studies closer to reality should be designed, in which doctors can select a vulnerable population, which is most at risk. In my opinion, in these populations, the new drugs are very efficient because the number needed-to-treat drops to very low values.”

CAN ANYTHING MORE BE DONE TO SLOW THE RISE IN ANTIMICROBIAL RESISTANCE AND CLOSTRIDIODES DIFFICILE INFECTIONS?

Antibiotics are used globally in supporting human health, the food industry, and in animal welfare. As such, antibiotic resistance is a One Health issue that can only be addressed through joined-up thinking that involves the collaborative effort of multiple disciplines working locally, nationally, and globally.^{3,34}

Both Cobo Reinoso and Guery highlighted the need for renewed and continuing publicity campaigns to remind the public and prescribers of the perils of antibiotic overuse. “When we talk about AMS, we tend to look at what is done in hospitals. But now, when you look at the use of antibiotics, the high numbers are not in the hospital; they are in the community. If we want to influence changes at a bigger scale, we need to reach the general practitioners. They are the ones prescribing larger number of antibiotics,” explained Guery. “So, we need more campaigns, like the one in France 10 years ago, ‘antibiotic: it’s not automatic.’³⁵ This was a great success because it was directed both at doctors and the general population and reminded people that in many situations, an antibiotic will not work.”

“It’s got to be a national policy, but it is complicated to do. There are many national, and international associations and all these organisations are trying to provide policies regarding antibiotic resistance and AMS. But all the stakeholders need to understand that information for general practitioners and the general public is vital and that *C. difficile* infection is only one of many indicators,” Guery emphasised.

Cobo Reinoso concurred and said: “AMS is an obligation, but it is not the only solution. Strategies must allow us to optimise what we have, use it better, achieve better results, but we need many more tools and resources. For example, in crowded hospital environments and overwhelmed workers with high workloads, it is not possible to achieve good hygiene practices.” Cobo Reinoso continued: “We need to invest to achieve quality. This is what managers and politicians need to understand. Do things very well, in the long term, it’s cheaper.”

"In some ways, this problem resembles the responsibility we should all assume in other areas such as pollution or climate change. What one

person can do alone is very little, but the sum of many can make a difference," concluded Cobo Reinoso.

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