in health care and in animal husbandry, immunising their population, and investing in water sanitation.[12] Additionally, high-income countries should have the responsibility—and interest—to spend the resources necessary to develop and implement better diagnostics that accurately detect CRE, and antibiotics effective against CRE that are also safe and affordable. For these solutions to have a global impact, collaboration among high-income countries and LMICs is essential.

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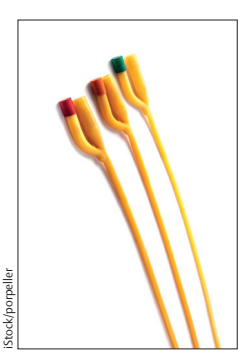
# Non-antibiotic prevention strategies against catheter-associated urinary tract infections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Health-care-associated infections are an important cause of morbidity, mortality, and prolonged hospital stay among inpatients, which result in substantial costs. Prevalence of health-care-associated infections among inpatients varies between 3·2% in the USA, 7·1% in Europe, and 15·5% in developing countries.[1–3] Catheter-associated urinary tract infection (UTI) is one of the most common health-care-associated infections. Yet, a substantial proportion of health-care-associated infections, especially catheter-associated UTIs (with a prevalence of 65–70%), are preventable[4]. It seems that the lower prevalence of health-care-associated infections in the USA than in Europe and in developing countries is mainly due to the reduction in the prevalence of catheter-associated UTIs and surgical-site infections through the implementation of national prevention programmes.[1] Therefore, prevention strategies for health-care-associated infections are essential; particularly, effective non-antibiotic strategies are urgently needed, since the prevalence of antimicrobial resistance is increasing and antibiotic consumption is its main driving force.[5,6]

In the *The Lancet Infectious Diseases*, Oyebola Fasugba and colleagues[7] studied the efficacy of 0·1% chlorhexidine solution for cleaning the urethral meatus before urinary catheterisation, a good example of a non-antibiotic prevention method. In a cross-sectional, stepped-wedge, open-label, randomised study, the authors showed that meatal cleaning with chlorhexidine (intervention population) before catheter insertion was superior to normal saline cleaning (control population) for the prevention of catheter-associated asymptomatic bacteriuria and UTI

during the 7 days after catheter insertion. The incidence of catheter-associated asymptomatic bacteriuria was 1·00 per 100 catheter-days in the control population versus 0·68 per 100 catheter-days in the intervention population (incident rate ratio 0·26, 95% CI 0·08–0·86; p=0·026). The incidence of catheter-associated UTI decreased by 94% after chlorhexidine cleaning compared with saline cleaning (0·06, 0·01–0·32; p=0·0080).

Fasugba and colleagues'[7] choice of catheter-associated asymptomatic bacteriuria as a co-primary endpoint remains questionable, because as The Infectious Diseases Society of America (IDSA) guidelines[8] for catheter-associated UTI stated, the relation between catheter-associated asymptomatic bacteriuria and UTI is unclear. It is often assumed that the presence of catheter-associated asymptomatic bacteriuria is necessary for the development of catheter-associated UTI, but most cases of catheter-associated asymptomatic bacteriuria do not result in—and can even be preventive of—catheter-associated UTI.[9] Furthermore, the number of catheter-days is the main risk factor of catheter-associated asymptomatic bacteriuria, with an incidence of 3–8% per catheter-day, so most patients with a urinary catheter are likely to develop it.[10,11] Therefore, the incidence of catheter-associated asymptomatic bacteriuria in studies is dependent on the number of catheter days and how often urine cultures are grown, and intervention studies aimed at preventing catheter-associated UTI should provide efficacy evidence by assessing the incidence of catheter-associated UTI as primary endpoint.

Furthermore, the authors have chosen to leave the decision of collecting a urine sample for bacterial culture to the treating physician, although urine is not usually sampled for bacterial culturing in asymptomatic patients. This might have resulted in the underestimation of the incidence of catheter-associated asymptomatic bacteriuria.

The authors did not include the economic evaluation of chlorhexidine cleaning in this Article,[7] although they plan to publish it in the future. We look forward to these results to know whether chlorhexidine cleaning is a cost-effective intervention in reducing catheter-associated UTIs, which would support the authors' recommendation to include the use of chlorhexidine for meatal cleaning before catheter insertion in guidelines for the prevention of catheter-associated UTI.

Another interesting point is patient censoring during the 7-day follow-up due to removal of the catheter.[7] In the control period, a lower percentage of catheters 52% (363/697) were removed before the end of follow-up than in the intervention period (79% [751/945]). Since a main risk factor for catheter-associated UTI is an increased number of consecutive catheter days, it is unclear whether a more frequent early removal of the catheter in the intervention period has introduced bias in the assessment of the primary outcome. In fact, the most effective way to reduce the incidence of catheter-assisted UTI remains the restriction of the use of urinary catheters and by removal of catheters as soon they are no longer necessary. This is assessed in the recent RICAT-study,[12] which is a quality-improvement project to reduce inappropriate use of catheters.

In summary, this study gives important evidence for the use of chlorhexidine solution for cleaning of the urethral meatus before catheter insertion to decrease the incidence of catheter-assisted UTI, but timely removal remains as another prevention strategy.

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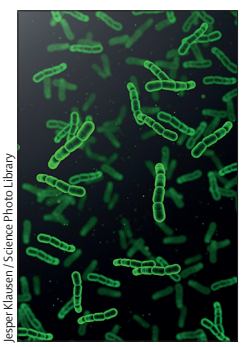
# One step closer to precision medicine for infectious diseases



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In *The Lancet Infectious Diseases*, Pierre-François Laterre and colleagues[1] present the promising results of a first-in-human study of CAL02, a novel antitoxin liposomal agent administered as an adjunct to antibiotic therapy in severe community-acquired pneumococcal pneumonia. Two doses of CAL02 were administered, with a 24 h interval. CAL02 consists of a mixture of small, empty, uncoated unilamellar liposomes that act as traps for a broad panel of bacterial toxins known to be inserted in cellular membranes.[2] Despite this study[1] only enrolling 19 patients into three groups (placebo, low-dose CAL02, and high-dose CAl02), more positive patient outcomes were observed in the high-dose CAL02 group compared with placebo. The advantages of CAL02 treatment were particularly obvious during the early course of the infection, when the bacterial load is high. We consider this study a medical breakthrough for two reasons.

First, animal and clinical studies have suggested that early sepsis mortality is caused by inflammation and infection-associated organ failure, whereas late mortality is due to immunosuppression, intensive care unit-acquired complications, and end-of-life decisions.[3,4] One possible reason for the low effectiveness of antibiotics on early mortality is that such drugs can kill toxin-producing bacteria but are unable to inactivate already-secreted toxins. Therefore, inhibition of toxin action might help to decrease early patient deterioration. Notably, there are several examples of toxin-targeted adjunctive treatments in patients with sepsis currently under development, such as extracorporal toxin adsorption and IgM-enriched immunoglobulins.[5-7] However, these treatments do not specifically eliminate bacterial toxins. They also inactivate damage-associated molecular patterns and pathogen-associated molecular patterns. Furthermore, extracorporal absorption removes pro-inflammatory cytokines.

Second, the global emergence of antibiotic resistance and the insufficient number of novel antibiotics are a major public health concern.[8] Accelerated development of novel antibiotics and antibiotic stewardship will certainly be of value in this crisis, but will not resolve it once and for all. Antibiotics kill bacteria and therefore impose selective pressure on the evolution of antibiotic resistance genes, not only in pathogens but also in the microorganisms that constitute a patient's microbiome. Microbiomes have been identified as a major reservoir of resistance genes that can be acquired by pathogens via horizontal gene transfer.[9] Consequently, many antibiotics can only be safely used for 15–20 years before resistance emerges.[10] Thus, we are trapped in a biological arms race between novel antibiotics and emerging resistance. A possible disruption of this vicious cycle could be achieved by non-lethal precision drugs that avoid collateral damage and inactivate or disarm the pathogen without killing. These requirements are fulfilled by virulence blockers, which target bacterial adhesion, bacterial toxins, or the quorum sensing system, resulting in decreased virulence without killing the pathogen or causing damage to the microbiome.

Although virulence blockers are a current focus of research into anti-infectives, the principle underlying them was originally discovered more than 120 years ago by von Behring and Kitasato, who observed that serum from vaccinated animals could inactivate those toxic compounds produced by tetanus bacilli.[11] In those days, clinical development moved more quickly than today. von Behring and Kitasato's research was published 11 days after their decisive experiment was completed; their first-in-human study was done 1 year later and, despite some drawbacks due to dosing issues, Hoechst started to produce and distribute the serum in 1892.[11] These results paved the way to tetanus and diphtheria toxoid vaccines that are still in use today.[11] Over time, the clinical use of CAL02 might also help to identify certain toxins with major contributions to the severity of infection, which can be further evaluated as vaccine targets.

There are dozens of virulence blockers in the early stages of clinical development and some have already received US Food and Drug Administration approval;[12]