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Lowbury Lecture

Lowbury Lecture 2021: tales of the unexpected in antibiotic resistance

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SUMMARY

Since the 1990s few new antibiotics have become available; during the same period the appearance and spread of bacteria no longer susceptible to first- and second-line antibiotics has accelerated; indeed some bacterial infections have become untreatable with existing antibiotics. Control of antibiotic resistance is multifactorial, and includes restrictive antibiotic use and good infection control. This lecture addresses three aspects of antibiotic resistance, with reference to the Netherlands, that illustrate the complexity of antibiotic resistance epidemiology. Initially selective decontamination of the digestive tract (SDD) was not adopted in the Netherlands because of concern about antibiotic resistance. However, three trials showed that SDD regimens, including four days of systemic cephalosporins, gave better clinical outcomes with no effect on antibiotic-resistant bacteria. Many predictions have been made about the impact of infections with antibiotic-resistant bacteria on human health. However, the situation is complex, because the risk factors for infection with multidrug-resistant bacteria are also risk factors for poor clinical outcome. A study in eight Dutch hospitals estimated the mortality attributable to antibiotic resistance as close to zero. Concern about the emergence of resistance in *Staphylococcus aureus* has limited the universal use of mupirocin to prevent surgical site infections. However, the risk may have been overstated, and universal decolonization with mupirocin and chlorhexidine has now become standard of care in patients undergoing cardiothoracic or orthopaedic surgery in many Dutch hospitals. Prophylactic antibiotics can improve patient outcomes with acceptable risks of promoting resistance.

Introduction

The discovery of antibiotics has changed medicine dramatically. Many bacterial infections became treatable and invasive treatment options became possible because of the protective effects of antibiotics. The significance of these new medicines was reflected by a continuous development of new antibiotics between the 1950s and the 1980s. At the same time there was a continuous increase in antibiotic use, as they were very effective, very safe, relatively inexpensive, and mostly used for a short period of time. Yet, because of their own success, development of new antibiotics gradually became less attractive for pharmaceutical companies. The existing business model is much more appealing for development of treatments of chronic diseases, and since the 1980s few new antibiotics have been approved by regulatory authorities. However, since

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Table I
Summary of three Dutch studies of selective decontamination regimens to prevent infections in ICU patients

Reference	Study design	No. of ICUs	Interventions	No. of patients	Outcome, no. (%), (95% CI)		
					ICU mortality	Hospital mortality	Day 28 mortality
De Jonge *et al.* [3]	Randomized controlled trial, with randomization to unit 1 or 2	2	Unit 1: SDD Unit 2: Standard care	466 468	Unit 1: 69 (15%) Unit 2: 107 (23%) $P = 0.002$	Unit 1: 113 (24%) Unit 2: 146 (31%) $P = 0.02$	—
De Smet *et al.* [4]	Cluster-randomized cross-over	13	Standard care SOD SDD	1990 1904 2045	443 (22.3%) 416 (21.8%) aOR: 0.87 (0.74—1.02)[a] 440 (21.5%) aOR: 0.81 (0.69—0.94)	632 (31.8%) 665 (32.6%) aOR: 0.85 (0.74—0.98) 584 (30.7%) aOR 0.88 (0.76—1.01)	544 (27.5%) 502 (26.6%) aOR: 0.86 (0.74—0.99) 546 (26.9%) aOR: 0.83 (0.72—0.97)
Oostdijk *et al.* [5]	Cluster-randomized cross-over	16	SOD SDD	5957 6040	1189 (20.0%) 1114 (18.4%) aOR: 0.84 (0.76—0.93)[b]	1677 (28.2%) 1589 (26.3%) aOR: 0.86 (0.78—0.94)	1530 (25.7%) 1439 (23.8%) aOR: 0.85 (0.77—0.93)

ICU, intensive care unit; CI, confidence interval; SDD, selective decontamination of the digestive tract; aOR, adjusted odds ratio; SOD, selective oropharyngeal decontamination.
[a] Odds ratios of intervention compared to standard care were calculated with the use of random-effects logistic-regression models to account for ICU-level clustering. All models for adjusted outcomes included the Acute Physiology and Chronic Health Evaluation (APACHE) II score (≥20 vs <20), age (>65 vs ≤65 years), intubation status during ICU stay, reason for admission to ICU (surgical vs medical), and sex.
[b] Odds ratios of SDD compared to SOD were calculated with mixed-model regression analysis. Adjusted odds ratios were corrected for age, sex, APACHE IV score, diabetes, chronic coronary insufficiency before ICU admission, and centre.

then the world has witnessed the emergence of infections caused by bacteria no longer susceptible to the regularly used antibiotics. In the last twenty years the appearance and spread of new variants of bacteria no longer susceptible to first- and second-line antibiotics has accelerated and in some settings physicians are now faced with bacterial infections no longer treatable with existing antibiotics. Within one century of the discovery of these miracle drugs, the post-antibiotic era no longer is a theoretical scenario.

There is large heterogeneity in the incidence of infections caused by antibiotic-resistant bacteria. In the developed world infections caused by the most difficult-to-treat bacteria mainly occur in hospitalized patients, and incidences of infections caused by antibiotic-resistant bacteria differ by country and by bug—drug combination. The Netherlands has, together with the Scandinavian countries, the lowest incidence rates of infections caused by the most prevalent antibiotic-resistant bacteria, such as meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), and carbapenemase-producing *Klebsiella pneumoniae* (https://swab.nl/en/exec/file/download/90).

The epidemiology of antibiotic resistance is driven by many variables and the success of a country such as the Netherlands to maintain low infection rates with such bacteria does not result from a single aspect. It is multifactorial, but restrictive antibiotic use and good infection control definitely contribute. The 2021 Lowbury Lecture addresses three aspects of antibiotic resistance, typical for the situation in the Netherlands, to illustrate the complexity of antibiotic resistance epidemiology, in which the obvious may not always be confirmed by science.

Antibiotics do more than cause resistance

Intensive care units (ICUs) frequently are the epicentres of antibiotic resistance. Here, antibiotic use is — necessarily — high, creating high selective pressure for resistant pathogens. Critically ill patients are susceptible to colonization and subsequent infection, and there are multiple opportunities for cross-transmission of pathogens due to the many physical interactions between healthcare workers and patients. Patients requiring mechanical ventilation are especially prone to opportunistic bacterial infections, especially of the lungs. Such ICU-acquired infections mostly occur after prior colonization of the respiratory or intestinal tract. In the 1970s the concept of selective decontamination of the digestive tract (SDD) was developed in patients suffering from haematological malignancies. Topical application of antimicrobials selectively affecting aerobic Gram-negative and -positive bacteria and yeasts, while at the same time sparing the anaerobic flora, was used to protect such patients from opportunistic infections [1]. The same pathophysiological patterns appeared relevant in mechanically ventilated patients in ICU. To protect patients from incubating respiratory tract infections at the time of intubation, a four-day course of intravenous treatment with a second- or third-generation cephalosporin was added [2]. Initial studies were too small for definite answers and the safety of widespread use of antibiotics for prophylaxis was questioned. Therefore, in the Netherlands (and other countries) SDD did not become standard of care treatment.

Three studies in Dutch hospitals have shifted the paradigm (Table I). All three studies had a cluster-randomized study design with SDD being applied unit-wide in all patients with an expected stay in ICU of several days [3–5]. In all three studies SDD was associated with a better outcome for patients, reflected in lower mortality rates in ICU, hospital, or at day 28. Of note, SDD resulted in an 85% increase in the use of cephalosporins at the unit level, due to the universal four-day cephalosporin prophylaxis [3]. However, longitudinal analyses of antibiotic resistance in ICUs using or not using SDD revealed that widespread use of SDD was not associated with increased prevalence of infections or carriage with antibiotic-resistant bacteria, including ESBL-E [6,7]. Thus, SDD – containing topical application of tobramycin, colistin, and an antifungal agent (nowadays mostly nystatin) in combination with a four-day intravenous course of a cephalosporin – is now recommended in all patients admitted to ICU and with an expected ICU stay of at least three days. The concept of SDD was also investigated in ICU settings with higher prevalences of antibiotic resistance than in Dutch ICUs (https://swab.nl/en/exec/file/download/90). This higher prevalence mainly resulted from ESBL-E, and therefore universal prophylaxis with cephalosporins was not included in the SDD schedule in these countries. In this international cluster-randomized study SDD was, as compared to standard care without specific prophylaxis, not associated with reduced incidence of ICU-acquired bacteraemia or better patient outcome [8].

Antibiotic resistance: how bad will it get?

Antibiotic resistance is widely considered a global threat for human health. This is supported by equally widely cited studies quantifying the consequences of antibiotic resistance. The most well-known study is the O'Neill report which stated that, in the year 2015, 750,000 people died because of antibiotic resistance and that this would be 10 million per year in 2050 (https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf). Yet the methods and assumptions underlying these conclusions have been criticized and are most probably gross overestimates [9]. Methodologically more sound estimates were produced by the European AMR collaborative group, but these were also based on extrapolations of surveillance and estimates of attributive mortality because of resistance [10]. The latter is difficult to quantify accurately. For instance, the 30-day prognosis of patients suffering from bacteraemia caused by meticillin-susceptible *S. aureus* (MSSA) may differ considerably from that of patients with MRSA bacteraemia, and for many other reasons than the antibiotic susceptibility of the causative pathogens leading to inappropriate initial antibiotic therapy. In an international study, patients suffering from bacteraemia with MRSA had a four times higher likelihood of inappropriate empirical antibiotic therapy than patients with MSSA bacteraemia [11]. However, the likelihood of survival 30 days after bacteraemia was not influenced by antibiotic resistance or appropriateness of empiric antibiotic treatment, but by the age and comorbidities of the patients, and the severity of infection. The European AMR collaborative group estimated that, in the year 2015, 206 patients died because of antibiotic resistance in the Netherlands, mostly because of infections caused by third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*, aminoglycoside- and fluoroquinolone-resistant *Acinetobacter* species, and *Pseudomonas aeruginosa* resistant to at least three antimicrobial groups [10]. This estimate differs considerably from a study performed between 2013 and 2016 in eight Dutch hospitals that was designed to accurately quantify the attribution of antibiotic resistance to patient outcome [12]. In this parallel-matched cohort the estimated attributable mortality due to antibiotic resistance was close to zero, despite a 53% lower proportion of patients with infections caused by resistant bacteria receiving appropriate antibiotic therapy at the time of infection onset. Without down-sizing the relevance of antibiotic resistance as a global health threat, I think we need more detailed studies to accurately quantify the consequences of antibiotic resistance for patients in different healthcare settings and different countries.

Preventing post-surgical infections

Staphylococcus aureus is a frequent cause of post-surgical infections, and humans colonized with *S. aureus* in the nose are prone to such infections. It has been estimated that about one-third of humans are persistent nasal carriers of *S. aureus*, one-third are intermittent carriers, and the final one-third are persistent non-carriers [13]. Decontamination of *S. aureus* carriage before surgery was postulated as a logical and feasible preventive measure. Yet, initial studies testing the effect of nasal decontamination preoperatively failed to demonstrate convincing results, possibly because a large fraction of patients included was not colonized, and thus could not benefit from such an intervention [14]. In a placebo-controlled double-blind trial, only patients with documented nasal carriage with *S. aureus* were randomized [15]. Almost 90% of all patients underwent surgery and the use of nasal ointment with mupirocin and chlorhexidine showering reduced the risk of subsequent *S. aureus* infection with 58% and the risk of deep-seated *S. aureus* infection with 79%. These preventive effects were most obvious in patients undergoing cardiothoracic and orthopaedic surgery.

The results of this study provided high-quality evidence for implementing this intervention in standard care. Yet, implementing universal preoperative screening for nasal carriage with *S. aureus* in all patients scheduled for surgery, and providing medication in time in those colonized, appeared challenging. Universal treatment of all patients, without screening, would be more feasible and guarantee prophylaxis for all patients colonized with *S. aureus*. Such a strategy would, therefore, be more cost-effective than preoperative screening of individual patients [16]. The consequence of such a strategy, though, would be that many patients would be exposed unnecessarily to antibiotics, which would increase the selective pressure for resistant variants.

Indeed, staphylococci may develop resistance to high concentrations of mupirocin and this resistance is located on a mobile plasmid that is highly prevalent in coagulase-negative staphylococci [17]. It was hypothesized that increased usage of mupirocin would exert higher selective pressure for this plasmid to spread to *S. aureus*, creating high-level mupirocin resistance in *S. aureus* and render a cheap and effective preventive measure ineffective. In a series of experiments we investigated the in-vivo occurrence of interspecies transfer of this plasmid in patients carrying both coagulase-negative staphylococci and *S. aureus*, and we used modelling to determine the risks of different strategies [17–19]. It was concluded

that, with a low prevalence of high-level mupirocin resistance in *S. aureus*, the risks of interspecies transfer of resistance during short periods of mupirocin use, together with good infection control practices and continued monitoring of mupirocin resistance in *S. aureus*, were acceptable. As a result, universal treatment with mupirocin nasal ointment and chlorhexidine showering without screening for *S. aureus* carriage has now become standard of care in patients undergoing cardiothoracic or orthopaedic surgery in many Dutch hospitals.

Antibiotic resistance is a global health threat, and use of antibiotics, justified and unjustified, contributes to this risk; the more you use it, the sooner you lose it, they say. Yet, antibiotics do more than cause resistance. If supported by solid scientific evidence and with good epidemiological monitoring of patients, prophylactic antibiotics can improve patient outcomes with acceptable risks for increasing resistance.

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