EDITORIAL

Confronting complex infections in a tertiary healthcare setting

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Infections, particularly complicated urinary tract infections (cUTI), are responsible for a substantial part of emergency department visits in secondary and tertiary hospitals.[1,2] The Dutch Working Party on Antibiotic Policy (SWAB) has written guidelines for empiric antibiotic therapy for (c)UTIs based on antibiotic resistance rates to these drugs as monitored by Nethmap.[3] Are these guidelines, however, applicable to all Dutch healthcare settings? And more specifically, are these guidelines applicable to a tertiary healthcare setting, which often includes multimorbid patients with complicated UTIs? This is the focus of Wijting et al., who investigate both micro-organism distribution and susceptibility patterns.

In this observational retrospective cohort study, the authors show that the susceptibility rates of commonly isolated micro-organisms to empirical intravenous antibiotic therapy for patients with a cUTI in the emergency department of a Dutch university hospital is comparable to national epidemiologic data. Resistance to orally available antibiotics however, is higher for the most frequently cultured pathogens. A shortened time between presentation at the emergency department and last admission resulted in lower susceptibility rates of the isolated uropathogens to initiated antibiotic therapy, especially if readmission occurs within three months. Based on these data, the authors recommend treatment with empiric therapy as prescribed in national guidelines, which include cefuroxime (or a third-generation cephalosporin) and gentamicin. For strictly selected patients, e.g., with severely impaired renal function (eGFR < 30 ml/min) or renal transplants, they advise consideration of meropenem.

The article by Wijting et al. raises the concern of whether the tertiary healthcare setting is a risk factor for infections with resistant micro-organisms. Reports identifying independent risk factors for harbouring resistant micro-organisms, include the recent use of broad-spectrum antibiotics, health care exposures, and travel to parts of the world where multidrug-resistant organisms are more prevalent, as illustrated, for example, in the COMBAT study.[4-9] However, information is lacking regarding the Dutch tertiary healthcare setting as a risk factor. Thus, the authors provide valuable insight with their findings that susceptibility rates to cefuroxime/gentamicin drop well below 90% (the threshold that the authors also refer to for empiric treatment justification) in those who have been admitted to a tertiary healthcare setting within the previous 3 months, especially since these patients accounted for almost half of their studied population (40.3%). This could well reflect the increased risk of resistance attributable to tertiary healthcare settings and support the use of other antibiotic regimens to account for healthcare-associated flora. This includes for example, piperacillin-tazobactam/gentamicin, which is commonly used in these situations, although not discussed by the authors, and advised by institutional SWAB guidelines. A relevant follow-up question that Wijting et al. have not yet addressed in this study would therefore be to what extent antibiotic regimens should take the tertiary healthcare setting specifically into account in empirical therapy for cUTI in comparison to other healthcare settings. Such a follow-up study should also specifically define any identified highly resistant micro-organisms (HRMOs), such as pathogenic micro-organisms that are resistant to a combination of therapeutically-relevant antibiotics including first-line treatment choices.[10] The potential relevance of HRMOs in the tertiary healthcare setting as a risk factor for resistance is also illustrated by the difference in observed susceptibility to first-line orally available antibiotics such as fluoroquinolones or trimethoprim-sulfamethoxazol, compared to NethMap data. The risk of harbouring fluoroquinolone-resistant micro-organisms is driven by the prior use of fluoroquinolones.[11,12] Could the higher risk for fluoroquinolone resistance in the complex academic patient also be related to the academic setting or is it only

because of a higher chance of prior use of said antibiotics in these patients and settings? Nonetheless, additional studies including HRMOs would facilitate drawing better conclusions as to whether or not tertiary care is a risk factor for cUTIs with HRMOs, and what empirical regimen in which setting is best advisable, especially for those patients who are quickly readmitted.

We can extend the above concern to include other infections (e.g., pneumonia) after a recent admission to a tertiary healthcare setting, and the implications for definitions of hospital-acquired and healthcare-associated infections. The Dutch Working Party on Antibiotic Policy (SWAB) currently applies the definition of nosocomial acquired infection to infections acquired during a hospital stay (two days or more after admission) or acquired within 30-90 days after hospital discharge, regardless of the secondary/tertiary healthcare setting.[13] The potential difference in resistance rates between these healthcare settings touches a relevant point frequently encountered in daily medical consultation, which the authors also raised: until what point can we include cultural history into the choice of antibiotic therapy? Studies have already been published that carriership of a HRMO < 6 months is an independent risk factor for a repeat culture with HRMO, which will often lead to an HRMO-related infection.[12] The findings of Wijting et al. seem to support this statement with the lower susceptibility rates observed with a shorter time to readmission, although as mentioned, additional information on the HRMO in the studied population would be necessary. It is also important to note that previous resistance is a risk factor for resistance,[11,12,14] but a previously isolated susceptible micro-organism does not mean that the risk for resistance is lower. The fact that cultures have been previously taken increases the chance of antibiotic use, which is indeed, a risk factor for resistance. The question remains: should we extend the definition of terms such as healthcare-associated infections, or introduce a new definition to also account for the previous healthcare setting, in addition to the frequency and timing of admissions and culture history? This may be relevant for empiric treatments for certain patient categories with complex infections in the tertiary healthcare setting, including cUTIs, and warrants further investigation.

According to the authors, empiric antibiotic therapy is still sufficient for most cUTIs in a tertiary healthcare setting. Unfortunately, for patients most at risk for resistance (i.e., patients in tertiary healthcare settings with frequent readmissions or readmissions < 3 months) empirical therapy has the largest liability with perhaps even fewer safe options for specifying empirical regimens. In addition, options for oral antibiotics are limited, implying that these patients will have to be admitted and thus, potentially confronted with the tertiary healthcare setting as risk factor for additional HRMOs. What this will mean for the future is yet to be seen. Can we restrain this vicious circle with a policy of restricted antibiotic prescriptions? There is a need to continue to address this issue in order to combat antibiotic resistance, regardless of healthcare setting.

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