Antimicrobial Resistance Differs Significantly Between Hospitals
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**INTRODUCTION**

Sepsis is a life-threatening syndrome caused by a dysregulated host response to infection. In case of a suspected case of sepsis empirical antimicrobial treatment is needed. The choice of empirical sepsis treatment is primarily an "informed guess" based on national guidelines, but also on knowledge of local and regional resistance of typically isolated microorganisms. Therapy based on guidelines works best when there are no major differences in antimicrobial resistance. For the determination of the most successful therapy, intrinsic resistance of isolates must also be analysed.

**MATERIALS / METHODS**

In this study, we analysed bug-drug combinations of all bacterial blood culture isolates from patients from all 14 secondary and tertiary care hospitals in the Northern Netherlands in the last 15 years (from 2002 to 2016). The Netherlands consists of 12 provinces, of which the Northern three (Friesland, Groningen and Drenthe) contain a total of 14 hospitals all within a 30 km range of the other nearest hospital. Only first isolates were included. The isolates were selected using a novel selection algorithm, based on the M39-A4 guideline of CLSI, taking into account isolate-specific resistance to key antibiotics which were chosen based on the genus and Gram stain. Subsequently, we compared the resistance of blood culture isolates between hospitals using a full-region approach, by grouping the hospital locations by province (Friesland, Groningen, Drenthe). This allowed for reliable and anonymous analysis of antimicrobial resistance for any bug/drug combination. To calculate differences in antimicrobial resistance, the number of susceptible isolates ("S") for a specific antibiotic was divided by the total number of test results for that specific antibiotic ("S", "I" or "R"). Then results were compared with a G-test of goodness-of-fit. The

Using the novel selection algorithm, more than 10% more bacterial strains were included than with the application of the CLSI guideline, resulting in a total of about 113,000 instead of 98,000 isolates. For the same microbial species, we found significant differences in antimicrobial resistance between hospitals. However, as the years went by, the differences decreased. For instance, figure 2 shows all isolates tested for amoxicillin, illustrating that the resistance to amoxicillin varied greatly between 2002 and 2010 in the three provinces (p < 0.05), but since 2011 this difference diminished (p > 0.05, yellow bars).

**RESULTS (CONT.)**

Notably, the prevalence of Quinolone and Aminoglycoside Resistant Enterobacteriaceae (QARE) rose from 0.3% in 2002 to 5% in tertiary care in 2016 (figure 3). In particular, prevalence in tertiary care increased since 2008. Nevertheless, prevalence of QARE remains lower in than in neighbouring countries.

The distribution of Gram-positive and Gram-negative bacteria was related to the age of the patients. Older patients showed a higher prevalence of sepsicaemia caused by Gram-negative bacteria than younger patients (figure 4a). Figure 4b shows this difference without all coagulase negative Staphylococci.

To determine the best empiric therapy for sepsis, an overview of antibiotics that can be used are displayed in table 1, with their according resistance percentages.

**DISCUSSION**

Empiric therapy for patients with septicaemia might be improved in single hospitals, by analysing the regional/institutional epidemiology of bacteremic isolates comprising the correspondent resistance. It has been shown that there are major epidemiological differences in microbial resistance between provinces within our region. This allows for a more specific empiric therapy of first choice using local hospital protocols, rather than using general national guidelines. We recommend analysing bacterial surveillance and prevalence of resistance in a full-region approach instead of single hospitals or the national level, using the novel selection algorithm to include more relevant isolates and improve reliability of the analysis.