Testing of Resistance in relation to Infection control and Antibiotic use in the Netherlands, Getting Less problems by working together (TRIANGLE)

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TRIANGLE study:

Incidence density and clonality of Highly Resistant Micro-Organisms (HRMO) in Dutch hospitals and the relation with antimicrobial use and infection control.

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Background:

The increasing emergence and dissemination of HRMO is becoming a world-wide problem in hospitals (1). This can be caused by a patient carrying a resistant pathogen on admission, by horizontal transfer between patients, through selection based on antimicrobial use, and by transfer of resistance genes (2,3,4). The major factors of the development and spread of HRMO in a hospital are the selective pressure caused by the intensive use of antimicrobial agents and by breaks in infection control procedures. In 2005 the first definition of highly resistant micro-organism (HRMO) was published (5,6). In this paper HRMO were defined as micro-organisms which 1) are known to cause diseases, 2) have acquired an antimicrobial resistance pattern that hampers empirical therapy, and 3) have the potential to spread. The designation HRMO is, therefore, dependent on the bacterial species and the antibacterial agent(s) against which it has acquired resistance.

This definition can be used as a tool for assessing the scale of the resistance problem at a local, national or international level.

Study objectives:

The primary objective of this study is to determine the variations in the incidence density of HRMO in Dutch hospitals.

Secondary objectives are to determine the relative importance of clonal spread and spread of mobile genetic elements and the association between the incidence density of HRMO and

1) the amount of antimicrobial agents used
2) the kind of antimicrobial agents used
3) variations in infection control policies
**Methods & Materials:**

**Design:**
Prospective observational multicenter study.

**General information on participating hospitals**
For the entire hospital and for ICU’s separately: number of admissions, number of patient days and average length of stay

**General data on antimicrobial use:**
defined daily doses (DDD) and prescribed daily doses (PDD) for total use, and per group of antibiotics, according to the ATC/DDD index 2005 from the WHO Collaborating Centre for Drug statistics Methodology (7). A hospital pharmacist will co-ordinate the data collection.

**General data on infection control measures:**
Questionnaire on the implementation of infection control procedures including specific measures for patients with BRMO and general measures. An infection control practitioner will co-ordinate the study and assists in the local data collection.

**Culture & susceptibility methods:**
Per hospital the method of susceptibility testing and breakpoints that are used are registered for relevant bacterial species.

**HRMO data and strain collection:**
During 2007 and 2008 all HRMO from hospitalised patients are registered and stored at minus 80 degrees Celsius. For each HRMO the following variables are recorded: patient information (age, sex, medical speciality, ward), bacterial species, antimicrobial susceptibility data and source of the isolate. The date of admission and first date of isolation of the HRMO as well as the date of discharge are registered. Furthermore, it is scored if the patient has been admitted to the ICU 30 days before the isolation of the HRMO and if bacteraemia with the HRMO has occurred. Mortality at discharge is scored as well.
From all patients the first available HRMO of each species is stored. When multiple isolates from one species are found with differences in susceptibility pattern in one patient, only one is included in the study.

**Typing of HRMO**

All MRSA strains are stored and typing results from the RIVM are used for primary analysis. Other HRMO are typed using AFLP (8) or other methods to be agreed upon by the investigators. To determine the transmission of integrons a PCR amplification of the class 1, 2 and 3 integrase specific *intl1* and *intl2* genes will be performed on selected strains (9). Other methods can be used as well after agreement by the investigators.

**Definition of nosocomial or ICU-relatedness:**

HRMO strains cultured more than 72 hour after admission, or less than 72 hour after admission but shortly after discharge (within 30 days) are defined as nosocomial HRMO. Patients who are on an ICU or have been on an ICU, before the isolation of the HRMO, with a maximum of 30 days, during the same hospitalization are defined as ICU-related. Cross-transmission is defined as genotypically related strains occur in epidemiologically linked patients. Genetic relatedness was determined on basis of both visual and computerized interpretation of AFLP patterns. Epidemiological linkage was defined as two patients who have been in the same hospital location with a maximum time window of 4 weeks. Cross-transmission of integrons is defined as identical integrons that occur in epidemiologically linked patients. Intraspecies transfer of an integron is defined as two genotypically unrelated isolates of the same species carrying the same integron. Interspecies transfer of an integron is defined as two different species carrying the same integron. Intergenus transfer of an integron is defined as two different genera carrying the same integron.

**Data-analyses, quality control & statistics:**

Privacy of patients is provided by decoding all data according to the requirements of the privacy regulation in the Amphia hospital. The data are entered in a database and analysed using Excel and the Statistical Package for Social Sciences software (SPSS version 12.0). Statistical significance is accepted when the chance for coincidence was less than 5%.
References:


6. **WIP guideline, december 2005**

