



**Karolinska  
Institutet**

**Department of Laboratory Medicine, Division of Clinical  
Pharmacology**

## **Clinical studies on drug treatment of hospitalised patients: general infectious diseases and acute myocardial infarction**

**AKADEMISK AVHANDLING**

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## ABSTRACT

Treatment of hospitalised patients is generally governed by the pre-developed algorithms and common guidelines. These approaches are helpful in most, but not all cases. Treatment of hospitalised patients is limited to the time of hospital stay and is therefore directed to immediate help. There are diseases for which immediate help is as important as its long-term consequences. General infections and ischemic heart disease are among the most prominent examples. Cardiovascular diseases (CVD) remain the leading cause of death in developed countries. While immediate treatment of acute myocardial infarction (AMI) is currently dependent on rapid surgery and management of thrombosis, adequate long-term treatment with other agents including beta-blockers may prolong time to further cardiovascular events and therefore prolong patients' life. It is important to achieve adequate effects as early as possible and avoid adverse drug reactions (ADR) to fulfil primary goals of the treatment. Factors that affect individual treatment response may be inherited (genetic polymorphisms) or exogenous (drug interactions). General infectious diseases represent another problem where hospital lethality is traditionally high and is dependent on a number of factors, mainly timeliness of diagnosing and susceptibility of pathogenic microorganisms to available antibiotics. This susceptibility is a changing parameter and may be dependent on the pattern of traditional antibiotic use in a given hospital, which is related to selection of resistant pathogens potentially worsening patients' survival. This also has a more global consequence of cultivation of multiple resistant pathogens, which may then be spread over the hospital, region and even country borders.

General aim of the current thesis was to increase knowledge of specific factors that may affect quality of hospital care in the treatment of general infections and acute myocardial infarction and suggest methods to minimize their negative influence in hospitalised patients.

We found that CYP2D6 is a major factor of metoprolol disposition and effects in AMI patients and also a major determinant of individual variability of response to the treatment. Common exogenous medications prescribed for treatment of depression complicating AMI namely selective serotonin reuptake inhibitor (SSRI) paroxetine significantly increase metoprolol concentrations in patients and put them at risk of excessive bradycardia. Based on our findings we suggested that CYP2D6 genetically defined activity may be related to ventricular rhythm disorders (VRD) complicating early period after acute myocardial infarction, though not in patients undergoing percutaneous coronary intervention.

In our studies on surveillance of antibiotic use and resistance we applied a method of Drug Utilization 90% (DU90%), and modified it with cumulative microbial resistance data. From this combination it was clear that most widely utilized antibiotics are not suitable for treatment of registered infections due to high resistance of the microbes. We showed that this method of combined presentation of antibiotic 90% use and microbial resistance reflects existing situation in a comprehensive and easy way both – for prescribers and authorities. When this method was tested in a Russian hospital we observed antibiotic use and resistance during five consecutive years, we could not see any change in resistance despite obvious changes in utilization profile. We considered these changes attributable to our intervention because they were not observed in a control Russian hospital. We also observed antibiotic utilization and key microorganisms resistance in a Swedish hospital. Overall antibiotic use was much higher in that hospital, antibiotics active against multiple resistant microorganisms were present within DU90% segment, despite that resistance of key microorganisms in this segment was low during the whole observation period. We concluded that the instrument of combined presentation of antibiotic use and cumulative resistance is an effective tool to show in an easy and comprehensive way rationality of antibiotic use and change utilization profile. It was also clear that in hospitals with high resistance of microorganisms to the most agents used other methods of infection control are required.

Our studies demonstrate two principally different approaches to improvement of drug treatment of hospitalised patients. In cardiovascular diseases we showed clinical importance of pharmacogenetics and drug interactions, which may further be continued by studies defining place for pharmacogenetic tests in clinics. For patients suffering from general infections we proposed a more general approach of antibiotic use and resistance surveillance that will help to define existing problems. It is a crucial step to improved treatment of patients in a particular hospital but also may have global contribution to containment of world dissemination of resistant microbes.