CHARLES UNIVERSITY IN PRAGUE

THIRD FACULTY OF MEDICINE

Heidi Riddervold Mourud

Prevention of Nosocomial Infections

Diploma thesis

Prague, April 2010

Author of diploma thesis: Heidi Riddervold Mourud

Master's programme of study General Medicine

Advisor of the thesis: MUDr. František Duška

Department of the advisor of the thesis: Department of Anaesthesia and Intensive Care Medicine

Date and year of defence: 08.04.2010

Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

In Prague on March 23th, 2010 Heidi Mourud

Acknowledgements

I would like to thank my supervisor MUDr. František Duška, for the extra time he has used to help me write my thesis. I am further grateful for his advice and guidance through the writing of my work. I would also like to make a special reference to MUDr. Olga Dzupova (Bulovka Hospital), who had an excellent lecture; “Nosocomial infection”. It gave me allot of information and inspired me to write my thesis on this particular topic.

Table of contents:

Summary:

Nosocomial infection and the importance of its prevention where first recognised by Dr. Ingaz Semmelweis in the 1850s, who discovered the effect of hand washing and disinfectant. Nowadays, nosocomial infections are a common cause of mortality and morbidity affecting 5-10 % of all hospitalised patients. It is further a major economical burden, estimated to cost $ 4,5 billion per year in the USA.

The most common diseases occurring in hospitalised patients are urinary tract infections, pnemonia (VAP and HAP), catheter related bloodstream infections, surgical site infections and gastroenteritis. The most frequent and most important causative agents of these infections are Gram positive (Staphylococci, Enterococci) and Gram negatives (Enterobactericae, Pseudomonas, Actinobacter) bacterie.

There are different types of patient affected, but in general do they have one or more risk factors. These risk factors include immunocompromised host, prolonged hospital stay, severe underlying ilness, need for frequent medical intervention, prolonged treatment with antibiotica or the presence of invasive device, catheter or endotracheal tube. Previous antibiotic treatment is also a risk because it impairs normal symbiotic bacterial flora and allowing colonisation with multiresistant strains (MDR). Thus, ICU patient are frequently affected by nosocomial infections. In this group of patients is early recognition and prompt intervention extremly important to prevent the progression to sepsis and septic shock, but diagnostics is particulatrly challenging as signs and symptoms of nosocomial infection may be masked by underlying disease or pharmacologic sedation.

So, preventive measures are the clue to make a hospital safer and ICU in particular. It is stated that over 25% of nosocomial infections could have been avoided if preventive strategies were adhered to. Preventive strategies can be divided into general (hand-hygiene, disinfectant, barrier precautions, isolation, asepsis, antibiotic prophylaxis) and infection-site-specific strategies. Both groups of precautions are discussed in this thesis, with special emphasis on newer approaches, e.g. antibiotic coated devices, screening of patients suspected to be infected and prevention of multi-drug resistant pathogens (MDR).

The control of correct antibiotic administration and the introduction of new vaccines have both been applied to reduce the incidence of MDR pathogens. This is still an area which needs further research.

1. Introduction:

The term nosocomial infection refer to an infection that develops at least 48 hours after the patient is admitted to the hospital. [37] (The word nosocomial comes from Greek meaning: nosos=disease and komien= to care for.) Today hospital-acquired infections occur in about 5-10% of patients admitted to the hospital in the USA. [33] Thus these infections are widespread and important to address. They contribute to serious adverse events, including increased length of stay, additional treatment with antibiotics, susceptibility to further infections, sepsis, advanced medical interventions, disability and death. The center for disease control and prevention (CDC) has a National Nosocomial Infection Surveillance system (NNIS). This system receives monthly reports from hospitals in USA (more than 270 institutions). From their new report it was estimated that healthcare-associated infections account for ca. 1.7 million infections and 99,000 associated deaths each year. [4] In addition, the WHO states that nosocomial infections are one of the leading causes of deaths. [7]

They are also a burden economically, and are estimated to cost the USA over $4.5 billion per year. [20] These costs are mainly due to prolonged stay of patient and the need of further diagnostics tools and treatment. [29]

1.1. Defining terms:

During hospitalisation the patient is constantly exposed to microorganisms. But these interactions need not to result in disease. This will be determined by characteristics of the pathogen, such as intrinsic virulence, bacterial inoculum and resistance to antimicrobial treatment. [7] It is further important to distinguish between colonisation and infection. Colonisation is the presence of bacteria on body surface or objects without necessarily causing disease.

An infection, on the other hand is defined as an "*invasion of the body with organisms that have the potential to cause disease*." [31] Further may any infection progress into a more serious clinical picture, such as systemic inflammatory response syndrome (SIRS), sepsis and multiple organ failure (MODS). These syndromes must be diagnosed early and treated before it is too late. Definitions are made to easier recognise these syndromes when they occur:

SIRS (systemic inflammatory response syndrome) is diagnosed if the patient has >2 of the following criteria:

-Temperature >38 degrees or <36 degrees

-Heart rate >90 beats per minute

-Respiratory rate >20 breaths per minute or need for mechanical ventilation

-White blood cell count >12.000 cells/ml or <4000 cells/ml.

Sepsis; SIRS in association with bacterial infection proven with culture.

Severe sepsis is defined as sepsis associated with signs of failure of at least one organ. Depending on the organ affected, different manifestations exist.

(Hypotension in cardiovascular failure, hypoxemia in respiratory failure, oliguria in renal failure, and coagulopathy in haematological failure.)

Septic shock is defined as SIRS associated with hypotension, refractory to volume replacement, and requiring vasopressors. Septic shock is a type of distributive shock.

MODS (multiple organ dysfunction syndrome) is failure of > 2 organ systems.[3]

A hospital-acquired infection is usually a sequelae of treatment, diagnostic techniques or procedures that the patient receive to treat his or hers underlying illness that was the reason for admission.[33]

1.2. History of nosocomial infections:

"He rolled up his shirt sleeves and took an ancient frock from a cupboard; it bore signs of a chequered past, and was utterly stiff with old blood. On of these coats was worn with special pride, indeed joy, as it had belonged to a retired member of the staff. The cuffs were rolled up to only just above the wrists..." Leeds, England, 1884.

This was the condition in surgery, before the introduction and acceptance of antisepsis. And therefore, there is no surprise that surgery was followed by infections in ca 80% of procedures during the late 19th century. At this time, it was safer to undergo an operation at home than in the hospital. In the 1830's the term for hospital-acquired infections was introduced by James Simpson in England, who called the problem "Hospitalism." His theories were that poor ventilation and stagnate air were the main culprits causing nosocomial infection. The hospitals solved this problem by opening the windows and preventing overcrowding.

It was first in the middle of 19th century that hygiene was focused on. Dr Ingaz Semmelweis worked as a surgeon in Hungary in 1848. He was known as the "saviour of the mothers", when he discovered the reason for the high incidence of puerperal fever (mortality 10-35%) in the clinic ran by physicians compared to the second clinic, which was managed by midwives. Apparently, the doctors were studying anatomy on cadavers in the morning and then they proceeded straight to their patients without washing their hands. Semmelweis came up with the idea of hand washing and the use of an antiseptic solution (Chlorinated lime.) Surprisingly, he met a great deal of resistance despite that results showed decreased mortality connected to puerperal fever. (In one hospital the mortality of childbed fever where reduced to ca 1%.) It took another 40 years to accept Semmelweis' idea about the benefits of hand washing in preventing infections. [21]

Some years later (1860's) Louis Pasteur proposed his germ theory. The germ theory states that microorganisms are the cause of many diseases. This, which was not accepted in the beginning, has now become a cornerstone of modern medicine. [37]

In 1928 Alexander Fleming discovered that the fungus Penicillium inhibited the growth of Staphylococcus. With further research it was established that it could kill other bacteria as well, especially gram positive strains.[15] In 1941, Dr. Fletcher tried it for the first time and noticed the remarkable effect the drug had. Penicillin got the nickname "wonder drug". The fact that it was non-toxic to humans made it even more applicable in medicine. This was the beginning of a new era. The use of Penicillin became widespread and many thought that this was the end of bacterial infections. But it didn't take long before the first resistant strains of Staphylococci appeared. The first cases were discovered in 1943. And a few years later, in hospitals all over the world, they outnumbered penicillin sensitive strains. Overuse of the drug was the reason. An example of this was the spraying of air with Methicillin in infant nurseries to prevent infection.

During 1960's nosocomial infections were increasing instead of decreasing. This was believed to be due to the hospital staff and their relaxed behaviour against infections. They were all relaying on antibiotics. Another factor contributing to this increase was the growing supply of medical devices and new technology, leading to more invasive examinations and procedures. The growing hospitals, with their increasing medical staff could treat more patients in shorter time, which caused a higher circulation of patients through hospitals. This demanded a change in the

hospital settings. The Centres for Disease Control (CDC) proposed standardisation of procedures, and developed protocols to increase patient safety and decrease the risk of infections. They also acknowledged the importance of asepsis and antiseptics. And as improvements were made, infection rates declined. [21]

1.3. Epidemiology and Causative Agents:

Most hospital-acquired infections are caused by pathogens common in the general population, in whom they cause little disease compared to hospitalised patients. The patients in ICU are especially at risk to develop infections. The prevalence in ICU was 24/100 patient in UK hospitals.[18]

There are many potentially organisms which can cause nosocomial infections, including bacteria, viruses, fungi and parasites.

Bacteria:

They are by far the most common nosocomial pathogens. Their reservoir can be endogenous or exogenous. Endogenous bacteria are from patient's own flora and exogenous are often from another patient (cross infection), from hospital staff (infected or colonised) or from the environment such as air-conditioning and vaporisers.[7]

A further distinction can be made between commensal bacteria and pathogenic bacteria. *Commensal* bacteria, also called opportunistic, are part of normal flora and have a protective role by preventing colonisation by pathogenic organisms. They do not cause disease in normal or healthy settings. Only when introduced into unprotected tissue or if the patient is immunocompromised, they may cause infection. An example of this is when coagulase-negeative Staphylococci, which colonise the skin, gain access to blood via intravascular lines and cause infection. The same is true for Escheria coli found in GIT, causing urinary tract infection in catheterised patients. These two are the most frequent bacteria from this group causing nosocomial infections. *Pathogenic* bacteria are organisms with higher virulence, which cause infections regardless of host health status.

Historically, Staphylococci, Pseudomonas, and Escheria coli have been the most common culprits. Today, most common pathogens are:
Gram positives:

Staphylococcus aureus, which colonise skin and nose in humans. It causes a wide variety of diseases. They major concern is its resistance to more and more antibiotics. Streptococcus pyogenes was historically the first important pathogen in Semmelweis era. It is still of importance.

Gram negatives:

Enterobacteriacae (E.coli, Kleibsiella, Proteus, Enterobacter) are found in the GIT. They may colonise immunosuppressed patients and cause disease. Especially infections related to catheters and cannulas. These bacteria also show a growing resistance to antibiotics.

Pseudomonas aeruginosa are often found in hospital environment, especially in damp and water areas. They may also colonise GIT of hospitalised patients, causing disease when hosts defends is compromised. [7]

Viruses:

They are often transmitted by parenteral route (transfusion, dialysis, injections or endoscopy) or by faecal-oral route. Some important viruses include Hepatitis A, B and C, Respiratory syncytial virus (RSV), Rotavirus and Enterovirus. Others include CMV, HIV, Influenza virus and HSV and VZV. [7] Norovirus is common cause of outbreaks in hospital, especially during winter.

Parasites and Fungi:

Most fungi and parasites are opportunistic pathogens, causing infections during extended antibiotic therapy or in severely immunocompromised patient. Giardia lamblia is an example of a parasite that can be transmitted easily among hospitalised persons. It may also be connected with water contamination. Infection can result in asymptomatic carriage or symptomatic disease. [27] Fungal infections have lately become a more common cause of nosocomial infections, causing disease in 3,8 per 1000 hospitalised patient. Examples are Candida, Aspergillus, Fusarium, Trichosporon, and Malassezia. Candidiasis remains the most common type of nosocomial fungal infection. Risk factors for fungal infections include immunocompromised host, antibiotic treatment, chemotherapy, intravascular catheters, neutropenia, hemodialysis, or prior fungal infection.[35]

Sites of Infection:

The centre of disease control and prevention (CDC) has calculated the frequency of the different sites affected by nosocomial infection. This study showed that:

- 32 % of all nosocomial infections are urinary tract infections
- 22 % are surgical site infections
- 15 % are pneumonia (lung infections)
- 14 %are bloodstream infections [4]

It is stated that about 25 % of these infections could have been prevented, if hospital staff were taking proper precautions and were following hygiene guidelines when caring for patients. [33]

2. Method:

Prevention of nosocomial infection is a well-known topic and it has been studied for years. Surveillance systems keeping documentation about frequency, mortality and morbidity, both on an international (WHO) and a national basis are already fully established. This paper is written as a short overview of the topic. I will explain the pathophysiology behind the most common nosocomial infections and take special consideration on how to prevent them. The paper will only include data from developed countries, due to the completely different situations in the underdeveloped world.

I have used sources form the Internet, searched Pubmed, medical books, professional doctor's, lectures and reports by WHO. No formal meta-analysis was conducted.

3. Results:

Prevention of nosocomial infection should be a priority in all hospitals.
To prevent nosocomial infection, it is important to understand the mechanisms behind its development and the different strategies employed to prevent the transmission of microrganisms.

3.1. Role of surveillance systems

National surveilance was initiated in the USA in 1970. Since that time CDCs National Nosocomial Infections Surveilance (NNIS) system has provided hospitals with standarazid methods to collect and compare data on nosocomial infections.
A study was done that showed the efficacy of infection-control programs and surveilance. The incidence of nosocomial infection was decreased with 32% in comparison to hospitals without strategies where it actually increased by 18%. [12] There are also recommendations for local surveillance systems, especially in wards, such as ICU, which experience high frequency of infections. Local surveillance include continious collection, recording of data and feedback on the incidence of nosocomial infections.[18]

Furthermore, should all hospitals have an integrated and monitored infection-control-program. This program should include components that are aimed at decreasing the frequency of infections. These programs have proven to be very effective. They inform, educate and give feedback. Further they provide documentation and data, which can be compared between and within hospitals. [7] The key components in the program may vary between hospitals, but generally includes: limiting the transmission of organisms through adherence to the basic precautions (hand hygiene, glove use and aseptic procedures), isolation strategies and proper handling of waste. Other factors such as minimising of invasive procedures and identification and control of outbreaks are also included.

3.2. Types of Preventive Strategies in Hospitals:

There are various strategies, ranging from obvious to high-tech, that may be employed to minimise the occurrence of nosocomial infections and the emergence and spread of multi-drug resistant pathogens. These preventive measures can be divided into three categories. The first category concerns the hospital environment,

the second targets the prevention of the most frequent nosocomial infection and the last is aimed at the prevention of the development of multi-drug resistant pathogens.

1a. General preventive measures
    Hand-washing and alcohol disinfection
    Barrier methods
    Cleaning environment
    Isolation
    Aseptic techniques
    Appropriate use of prophylactic antibiotics

2. Prevention of specific nosocomial infections

3. Reduction in multi-drug resistant pathogens
    Antibiotic policy
    Infection-control program [18]

3.3 General preventive measures:

There are some preventive measures that are known as universal or basic precautions. These basic procedures apply when handling all patients, regardless of suspected or confirmed diagnosis or infection status. They are important to prevent the transmission of microorganisms and to protect the patient. The most frequent route of transmission is by direct or indirect contact. Direct contact involves body surface to body surface and it may happen in all forms of daily patient care. Indirect transmission involves contact between the patient and a contaminated object. In general, for transmission to occur the host must be susceptible and the other person infected or colonised with bacteria (hands, nose, throat.) [37, 9]These universal procedures are based on the principle that all body fluids, non-intact skin and mucous membranes are potentially infective. Implementation of these to all patients will reduce the risk of infection from both known and unknown sources and is a prerequisite for an effective control of infection. [9]

The basic procedures include:

1. Hand hygiene is considered a key element in the prevention of direct transmission of pathogens. This was the first international request supported by WHO and the

World Alliance for Patient Safety.[18] Washing hands thoroughly, especially between contact with different patients and after contact with blood or other body fluids, should be routine. Also after handling equipment or articles that may have been contaminated. Hand washing might seem like something simple, but it is often done incorrectly. Thus it is important to educate staff and remind them about the importance of hand hygiene.

2. Barrier precautions: Gloves have an important role in reducing the transmission of microorganisms. Hospital staff wear gloves for different reasons; most importantly they provide a protective barrier and they prevent contamination of hands when handling material such as blood, body fluids, secretions and excretions. Their protection of contamination with blood-borne organisms is extremely important when handling patient with HIV, Hepatitt B or C. Gloves also protect the patient from those organisms colonising hands of hospital personnel. Thus gloves should be used during the application of invasive device and aseptic procedures, and during patient-care, especially if it involves the patient's mucous membranes or nonintact skin. Gloves must always be changed between patients and hands should be washed after gloves are removed. Wearing gloves does not replace the need for hand washing, because gloves may have small, non-apparent defects or may be torn during use, and hands can become contaminated during removal of gloves. [9, 28, 37] There was done a study to assess the protective effect of gloves during surgical procedures. The study concluded that depending on duration of wear, surgical gloves developed microperforations not immediately recognised by staff and this created a route for transmission of microorganisms. [13] Other strategies used to create a barrier for transmission are: Mask, eye protection and face shield. They are used during procedures that are likely to generate splashes or sprays of blood or other body fluids and secretions. The usage of masks also protects the patient from droplet or airborne transmission of bacteria during close contact between hospital staff and patient. Gown is used in procedures or patient-care where there is a likelihood of contamination of health care worker and during surgical procedures to protect the patient.
3. Environment: All equipment used in patient-care must be cleaned and reprocessed properly before it comes in contact with other persons. Needles and other sharp objects must be handled with care to prevent injuries and transmission of blood-born infections. There are established routines and guidelines in hospitals for

handling of waste and contaminated materials. Every hospital should also have adequate procedures for routine care, cleaning and disinfection of environmental surfaces. [28]

4. Isolation. There are two types of isolation. The first is “protective”, and includes the isolation of immunocompromised patients to reduce risk for opportunistic infections. The reasons for decreased immunity can be many. It can be physiological, due to extreme of age and malnourishment or it can be due to diseases (DM, cancer, liver cirrhosis, AIDS.) Also the increasing use of immune-suppressant drugs (corticosteroids, chemotherapy) may contribute to a less effective immune system. The second type of isolation is “source isolation”. Here the infected or colonised patient is isolated to prevent the transmission to staff or other patients. It is considered gold standard to isolate the infected patient in a single room. This can be problematic sometimes due to limited space. [18] And also crowded conditions and the necessity to transfer patients between units can make this difficult to manage.
5. Asepsis describes a condition in which living pathogenic organisms are absent, creating a state of sterility.[31] Antisepsis is the use of chemical solutions or disinfectants to reduce the number of microbes present on skin. To reach a state of asepsis varies techniques are being used, including surgical hand washing, scrubs, sterile clothes/gowns, clean room and sterile instruments. The proper preparation of patient with shaving, cleaning and applying of disinfectant is also important.[3] The application of invasive devices, such as endotracheal tube (mechanical ventilation), catheters (urinary and central venous) and surgical drains are increasing. Devices can easily become colonised and due to their disruption of host’s normal protective barriers they allow microorganisms to pass into tissue where they don’t belong and with the potential to cause disease. This has made the proper use of aseptic precautions even more important.

   First, something simple as *cleaning* will be mentioned**.** Where the aim is to remove visible dirt. The use of soaps or detergent diluted in water remove microorganisms from the object due to the mechanical action (because neither posses antibacterial action). Thorough cleaning can remove up to 90% of microorganisms and increase the effect of disinfection and sterilisation carried out afterwards. It must be done in a standardised manner to be effective. *Sterilisation* can be achieved by physical and chemical means and it means that the object is

free of microorganisms. Physical methods are based on the action of: heat (autoclaving, dry thermal or wet thermal) or radiation with gamma rays. Chemical methods include gas sterilisation with for example ethylene oxide. *Disinfection* is the application of a solution to an animate or inanimate surface.

Three distinctions can be made based on the guidelines from CDC:

High level disinfection: can be expected to destroy all microorganisms, with the exception of large quantity of spores. Intermediate disinfection: inactivates mycobacterium, vegetative bacteria, most viruses and fungi. Do not necessarily kill bacterial spores. Low level: Kill most bacteria, some viruses and some fungi. Can not be relied on to kill resistant bacteria and spores. Often the more active the disinfectant, the more toxic it is. Toxic solutions can be applied to inanimate surfaces, but for human skin the less toxic alternatives should be used. Thus there is no ideal disinfectant. It must be chosen according to the individual situation. Solutions include alcohol, iodine, chlorhexidine, hydrogenperoxide and others. [28]

6. Antibiotic prophylaxis: Chemoprophylaxis is used only when it has been documented that benefits are greater than risks. Some of the indications are selected surgical procedures, persons at risk of infective endocarditis (patient with mechanical heart valves) and in severely immunocompromised patient where the chance for infection is higher.[28] There are conflicting result when it comes to VAP and administration of antibiotic prophylaxis. There exist some clinical evidence that aerosolised antibiotics could prevent VAP, but they are weak. The concerns about high cost, resistant bacteria and other potentially risk factors of aerosolised antibiotics led several evidence-based groups to recommend against routine use of antibiotic prophylaxis.[22]

Surgical operations are classified according the purpose of antibiotic prophylactics. The indications for antibiotic prophylactics can vary between different hospitals, but in general this classification can be followed.

1. Clean: includes procedures that are performed in normally sterile tissue.

Examples are orthopaedics, neurosurgery and cardiovascular procedures.

The incidence of SIS is <2% and antibiotic prophylactics is not indicated. The exception is insertion of prostethic devices (knee or hip arthroplasty), where antimicrobial agents are given because an infection here would be disastrous.

2. Contaminated: included gastrointestinal, respiratory and genitourinary tracts. Here antibiotics are given for 48 hours.

3. Infected: here it will be appropriate with antibiotic treatment instead of prophylactics, because an infection already exist.[8]

The prophylactics should be given IV and within one hour prior to the intervention. Administration of antibiotics for longer time before a procedure is counterproductive, as there will be an increased risk for infection by resistant bacteria.[7]

3.4. Prevention of specific nosocomial infections:

3.4.1. Urinary tract infection

This is the most common hospital acquired infection. It is related to the use of urinary catheter in 80%. Fortunately this infection is associated with less morbidity than the other infections. In average, it prolongs the hospital stay with 3,8 days. [20]

The aetiology is ascending gram-negative bacteria (E.coli, Kleibsiella and Proteus). They cause infection by colonising the catheter, which bypasses the normal barriers of the patient. It creates a direct route for the bacteria into the bladder.
(Candida may also cause infection, more commonly in immunocompromised hosts.)
Risk factors for development of UTI are prolonged catheterisation, diabetes, female sex and age above 50 years.[8]

Prevention: Catheterise only when necessary. The insertion should be atraumatic and done under sterile conditions. The drainage of urine should be closed (standard). Maintain good patient hygiene to prevent the contamination and colonisation of bacteria. The catheter should be changed with appropriate intervals. Intervals depend on the development of symptoms or not. If no symptoms it can be kept for ca 3 weeks. If symptoms, such as dysuria, change of colour or blood in urine, it should be changed at once. In some patients it can be convenient to screen the urine for bacteria (in some ICU settings) at appropriate intervals. 8

3.4.2. Hospital acquired- and Ventilator associated pneumonia:

Nosocomial pneumonia is divided into two groups. The first group includes patients on mechanical ventilation causing ventilator-associated pneumonia (VAP).

The other group is patients without any ventilator support causing hospital-acquired pneumonia (HAP). In both groups, the existences of one or more risk factors for developing pneumonia are often found. Risk factors include mechanical ventilation (high risk, 30% gets pneumonia), extreme of age, severe underlying disease, immunodeficiency, depressed sensorium, cardiopulmonary disease, immobility, broad spectrum antibiotics and dysphagia.[38] The mortality ranges between 30-50%. It is highest in elderly and ventilated patients.

VAP:

This account for the most frequent hospital acquired infection in ICU patients, and is a leading cause of death. These patients are at higher risk for infection because the endotracheal tube or tracheostomies bypass host respiratory tract defence mechanisms and allow bacteria to be deposited directly into lower respiratory tract.
Other risk factors are the quality of respiratory care, the severity of patient condition and previous use of antibiotics. [8, 38] In VAP the source of infection may be either endogenous or exogenous. The exogenous source can come from contamination of respiratory equipment or directly from hands of hospital personnel.[7] The mechanism of endogenous infection is believed to be due to the passive regurgitation of colonised gastric fluid into the oesophagus. This is followed by micro-aspiration, which bypasses the endotracheal tube-cuff and gets into trachea and lungs of a recumbent, mechanically ventilated patient. It affects up to 50% of these patients.

Prevention: Avoid intubation when possible. It is extremely important with good oral hygiene in these patients to decrease the colonisation of upper respiratory tract and subsequent aspiration of subglottic secretions. Endotracheal tubes with a subglottic suction port reduce VAP, but may contribute to mucosal trauma.[18] When exchanging or handling the ventilator circuit hands should be cleaned and sterile equipment used. [8] Further should the patient be elevated to semirecumbent position and maintain stomach acidity (pH under 4), to prevent passive regurgitation of refluxed content into lungs.
Another preventive strategy is selective decontamination of digestive tract (SDD).
The thought behind this is that colonisation of GIT with potentially pathogenic bacteria can translocate from gut to oropharynx and cause pneumonia. The systemic administration of Cephalosporin to eradicate community-acquired infection and the topical administration of non-absorbable antimicrobials into GIT is the technique. The

aim is to remove all pathogenic strains while preserving the normal flora. There are concerns about the emergence of resistant strains with this technique. During the last 20 years, there have been over 56 studies conducted in around 10 000 patient. These studies demonstrated a reduction in mortality and morbidity without promoting the development of resistant organisms. However there is still no international consensus about the use of SDD in ventilated patient. [18]

HAP:

It is ranged third among nosocomial infections (15%) in USA and the prolonged stay is calculated to be on average 5,9 days. [20] The aetiology is often endogenous, and includes microorganisms colonising stomach and upper airways and mouth. The resultant infection is thus often mixed with bacteria such as Pneumococcus, Hemophilus, S.aureus, Enterobacteria and Pseudomonas.[7,38]

Other microorganisms affecting the lungs are viruses, especially Respiratory syncytial virus (RSV) causing bronchiolitis in children. Where Influenza virus is more frequent in elderly patient. This viral infection posses a risk for secondary bacterial infection (superinfection) of the lungs. With severely immunocompromised hosts, organisms such as Legionella and Aspergillus may be the etiological agent. [7, 38]

Prevention: different breathing exercises and cough techniques, correct position of patient in bed (semirecumbent, 30 degrees) and early mobilisation are recommended. In some cases, the need to increase analgesics may be needed to keep the patient motivated and pain free when mobilised. The patient should be educated and explained why these activities are important to get a better compliance. [8]

3.4.3 Catheter related bloodstream infections:

Catheter-related bloodstream infections (CRBSIs) are an important cause of nosocomial infection, especially in the ICU, where patients frequently have invasive device. It was estimated by the CDC a rate of 1,8-5,2 bloodstream infections per 1000 catheter days. It is likely that they cause a substantial number of deaths in hospitalised patients.[18] The average of prolonged stay varies from 7-24 days.[20] The source of infection is most frequently due to contamination of the catheter, either during its

insertion or it can be contaminated later from the patient's skin. Thus bacteria constituting the cutaneous flora are most commonly encountered. These are coagulase-negative staphylococci (S.epidermidis 60-90%), S.aureus and Candida.[8] Enterococcus and gram negatives can also be found in some situations. The main risk factors are the length of catheterisation, improper insertion, and poor post insertion care.

Prevention: There exist a six-step strategy that can be followed to reduce the occurrence of these infections. It includes antiseptic hand washing, including disinfection, full aseptic precautions and use of chlorhexidine during insertion. Further should the femoral route be avoided if possible and keep days of catheter placement to a minimum. Other preventive strategies are the impregnation of the catheters with antibiotics, either minocycline-rifampicin or silver sulfadiazine. This is recommended in high-risk patients and patient with long-term cannulation. The major concern here is the potential to induce multi-drug antimicrobial resistance. The use of ultrasound during insertion is good in difficult cases and in inexperienced doctors. It will reduce the formation of hematoma and misplacement, and could therefore decrease the risk of infections.[18] When opening of the IV line it should be strictly aseptic, and the time it is open should be minimised. Care at the insertion site with the maintenance of adequate hygiene and dressings and the frequent inspection to identify any change in the area around the catheter are of importance. The catheters should be replaced with regular intervals to reduce chance of colonisation and infection. Peripheral catheters can be changed every 48-hour and central catheter every seventh day. If any changes occur before, the catheter is removed and tip of catheter is send to microbiology for culture. Changes to be aware of include local signs of inflammation and systemic signs such as fever and rigors. In a patient with fever of unknown origin (FUO) and with CVC, hospital staff should always suspect catheter-related sepsis. [7, 8] Patient receiving total parenteral nutrition (TPN) through CVC lumen has increased risk for CRBSI. If the TPN is with high glucose concentration, the doctor should also keep in mind the possibility of Candida infection. [8]

3.4.4. Sinusitis**:**

Again, the presence of invasive device (nasogastric or endotracheal tube) contributes to the development of sinusitis. Sinusitis is a further risk factor for VAP. This is because the sinuses serve as a reservoir from which the microorganisms may

seed the respiratory tract. Clinical signs are often few, and fever together with purulent nasal discharge may be only presenting features. The incidence varies according different criteria used for the diagnosis; also it is higher in patient with nasotracheal tube compared to endotracheal tube. In general it is estimated to occur in 20-30% of patients who are intubated for over one week. The aetiology is mainly gram negative bacteria, such as Pseudomonas aeruginosa, Actinobacter and Enterobacteriaceae, but Staphylococcus and yeast may also cause sinusitis. [2, 11]

3.4.5. Acalculous cholecystitis

The inflammation of gallbladder without the presence of stones is more frequently encountered in critical ill patients, especially those on mechanical ventilation or those with sepsis or severe burns. It accounts for 5-10% of all cases of acute cholecystitis. It is associated with higher morbidity and increased risk for developing gangrene and perforation of the gallbladder. The mortality is also higher in acalculous cholecystitis (10-50%), compared to calculous disease (1%). Critically ill patients are at risk because they often have fever, are dehydrated and don't receive oral feeding. This leads to increased viscosity of bile, bile stasis and lack of Cholecystokinin-induced contraction of gallbladder. Thus another group of patients at risk for acalculous cholecystitis are those on total parenteral nutrition (TPN). Also the decreased blood flow to gallbladder wall, due to centralisation of blood occurring in severe infection and shock, contributes to the development of ischemia and subsequently inflammation. [30]

3.4.6. Surgical site infections (SSI):

SSI is infection in the site of surgery (wound infection). Incidence varies from 0,5- 22 % depending on type of operation and general state of patient. The same is true when it comes to the aetiology agent. But in general are S.aureus, coagulase-negative Staphylococci, Enterococci, E.coli, Pseudomonas and Enterobacter most frequently encountered. The development of SSI prolongs the stay by ca 7, 4 days.[20] Factors influencing SSI are the patient's general health, especially the existence of underlying diseases (diabetes, malignancy, malnutrition and obesity).

Others are the operation, surgical teams, postoperative care and antibiotic prophylaxis. The presence of foreign bodies or drains and the intrinsic virulence of the microorganisms are additional factors influencing the occurrence of SSI.

Prevention can be divided into 3 phases.

Preoperative: Minimise the stay of patient in hospital before the procedure. Be sure that the area being incised is shaved and properly cleaned. Antibiotic prophylaxis is given when indicated. The surgical team and the operation room are prepared after aseptic procedures.

Intraoperative: Use correct techniques, ensure bleeding control, excise devitalised tissue and remove foreign bodies. Keep surgical staff to a minimum, and follow aseptic procedure.

Postoperative: Aseptic care of the site, insert drain if necessary. The type of drain used depends on the site drained. If it is potentially infected, open drain will be applied. If it is draining a sterile place, a closed drain is often used. The wound should then be covered with sterile dressings. [8]

3.4.7 Other infections**:**

Skin and soft tissue infections: Open sores (ulcers, burns and bedsores) encourage bacterial colonisation and may lead to systemic infection. Thus proper wound care should not be omitted.

Gastroenteritis: This is the most common nosocomial infection in children, where Rotavirus is the main pathogen. In adults, gastroenteritis is often due to Clostridium dificile. [38] It is well known that administration of antibiotic per os, especially Clindamycin, Ampicillin and Cephalosporin, kill normal protective bowel flora and allow C.dificile and its toxins to produce disease (Pseudomembranous colitis or antibiotic associated colitis).[8] This should be kept in mind when these antibiotics are used. Outbreaks of gastroenteritis can also occur in hospitals. The Public health service for communicable disease surveillance has collected data in the period from 1992-2000 in England and Wales. They found that 79% of all Norovirus outbreaks were in healthcare institutions (40% in hospitals) and that these institutions had a peak during wintertime. These outbreaks were also associated with higher death rates and longer duration of the disease. This data thus show the impact Norovirus has in health service settings due to the vulnerable population residing here. A distinct outbreak pattern in health-care institutions suggests a combination of host, virology, and environmental factors that mediate these divergent epidemiological patterns.

Norovirus affect all age groups with the highest incidence in children <5 years and elderly.[19]

3.5. Preventive strategies to limit the development of MDR pathogens:

Bacteria can develop resistance towards antibiotics. This is a problem in both the community and in health care facilities.[7] The ways a pathogen may become resistant to antibiotics can be divided into intrinsic or acquired. Intrinsic resistance may be due to the lack of the molecular target for an antibiotic or that the membrane is impermeable to the agent. Acquired resistance is principally due to one of four mechanisms: drug inactivation, reduced permeability, drug-efflux or target modification.[18] Many of the bacteria causing diseases in hospitals have a high level of resistance to antimicrobial therapy. This is due to the fact that many patients receive antibiotics, especially broad-spectrum, when hospitalised. They are administrated both for therapy and as prophylactics. An example is in ICU, where ca 60% of patients receives antibiotics at any given time. This makes ICU a natural environment for the development of resistant pathogenic strains. Of concern are Staphylococci resistant to Methicillin and Vancomycin (MRSA, VRSA), Vancomycin-resistant Enterococci (VRE), ESBL-producing Klebsiella, Enterobacter, Pseudomonas and Acinetobacter.[18] There were an estimated 94,360 invasive MRSA infections in 2005, with ca 18,650 deaths. MRSA now kills more people annually in the USA than AIDS and breast cancer combined.[21] Thus the prevention of resistance in bacteria is becoming more and more important due to the growing problem.

There is a wide national difference of multi-drug resistance. In Europe, microbial resistance data is collected by the EARSS programme (European Antimicrobial Resistance Surveillance System) funded by the European Commission. This system tests antimicrobial susceptibility in different countries. The collected data provide national results for comparison.[18] This documentation keeps hospitals informed about the prevalence of resistant strains in their region.

The Antimicrobial Use Committee, is a committee that provides information about the appropriate use of antibiotics. They recommend, guide and educate hospital administrations by developing antibiotic-control policies. Further, they receive documentation from hospitals about antimicrobial administration and trends during a given period.

All these measures contribute to an overview of how and when antibiotics are administrated.

Hospitals often develop their own antibiotic policy and program. Here they inform about the appropriate use, according to dose, choice and duration. Other general recommendations in antibiotic policies, include the limitation of topical antimicrobials, administration of narrow spectrum when possible, avoidance of combination of antibiotics if not necessary and the obtainment of appropriate specimen for microbiological examination before any treatment is initiated. [7] These programs and policies are believed to decrease the inappropriate administration of antibiotics, thus reducing the development of resistant bacteria.

Another problem arising is the interchange of patients between hospitals and community, and the widespread use of antibiotics means that many multi-drug resistant organisms are now found in non-hospital environments.[18]

Lastly, and not to forget, are viruses and fungi. They may also develop resistance to treatment, and this may be of concern due to the lack of other treatment options for these organisms. An example is Herpes virus, which has been reported to be resistant to Acyclovir and Ganciclovir. HIV positive patients are most affected by this. Pathogens with intrinsic resistance often have somewhat lower virulence and thus they cause disease in patient already immunocompromised. Another example is Candida albicans, which has proven to be resistant to Amphotericin B. [33]

Vaccinations. As antibiotics only are effective against bacteria, vaccines were developed to target viruses, including smallpox, measles, mumps, typhoid fever, rubella, diphtheria, tetanus, yellow fever, pertussis, and poliomyelitis. Advancements in antiviral drugs were made starting in the 1970s with the introduction of Acyclovir to protect against herpes and cold sores In Norway we have a vaccination program which was started in 1952, and it is recommend today that all children should be vaccinated against 10 different diseases:

-DTP combination vaccine against diphtheria, tetanus and whooping cough
-Hib vaccine against Haemophilus influenza type b infection
-Vaccination against pneumococcal disease
-Vaccination against poliomyelitis
-MMR combination vaccine against measles, mumps and rubella
-Vaccination against human papillomavirus (HPV, from 2009)

Vaccine against tuberculosis (BCG vaccine) is no longer in the vaccination program. This was started from the school year 2009/2010. The vaccine is now only

offered to children with increased risk for TBC infection. The same holds for Hepatitis B vaccination.

A special indication is for all health care workers to be vaccinated against Hepatitt B and Hepatitis A. This is due to the increased risk for infection when exposed or handling patient's body fluids, secretions and excretions.

In addition to vaccines that are part of the childhood vaccination program, it is offered a variety of other vaccines such as influenza vaccine, and the different vaccines for travelling. [9]

3.6. Early recognition of nosocomial infections:

Depending of type of disease, there are some common manifestations of infection that often are present. The diagnosis and recognition of the disease mentioned in the text (UTI, HAP, SSI, CRBSI, gastroenteritis) can be quite easy to recognise if they present with their classical symptoms and signs, and if in patients who are not of extreme age or sedated. However, this is not always the case and sometimes the only reliable and obvious sign is fever.

Thus a change in temperature (increased/decreased) should always alert a physician that something is wrong. The occurrence of fever is a frequent finding in hospitalised patients, and especially in ICU patients. In the critically ill it should be taken even more seriously and call for an urgent response. This is due to the increased risk of progression into a more severe clinical picture, such as sepsis. Further, are patients in ICU often deeply sedated and the presence of medical devices (mechanical ventilation, urinary catheter, invasive device) makes it difficult for patient to report symptoms and for the physician to see or find them. [11]

Recognition of sepsis: Sepsis is an acute clinical syndrome that needs prompt recognition and resuscitation. The syndrome reflects the response of the host and not the actually cause. Thus the immediate threat for the patient is not only the uncontrolled growth of bacteria, but also the consequences of the systemic inflammatory response. The biochemical process of sepsis is complex and includes the activation and interaction of different mediators of the immunesystem, coagulation cascade, vasoactive mediators and acute phase reactions. The result is vasodilatation, loss of endothelial barrier, occlusion of capillaries and impaired myocardial contractility, which all leads to insufficient perfusion and reduced oxygen delivery to tissues, producing the clinical picture. The criteria of SIRS are often

present and should alert a physician to look for the cause and primary site of infection by history, physical examination and tests, including urinalysis and urine culture (particularly in patients who have indwelling catheters), serial blood cultures, and cultures of other suspect body fluids. As sepsis progress, signs of changed mental status (confusion or deceased alertness) develop, blood pressure starts to fall and oliguria can often be noticed. The increase of BUN and serum creatinine indicates the failing of kidneys and the progression of renal insufficiency The patient often hyperventilates to compensate for the raised level of lactic acid, which occur in shock due to the anaerobic metabolism. This cause a low PaCo2 and manifestations of respiratory alkalosis. As shock progresses metabolic acidosis develop and pH decreases. The progression to shock indicates that body's compensatory measures have failed. [23, 25]

4. Discussion:

As already mentioned, there are many different types of preventive strategies used to reduce the occurrence of nosocomial infections. The WHO states that persons are the main source of microrganisms, and that hand hygiene is one of the most important preventive measures. Secondly, invasive devices are being applied more frequently than before, and these infections now account for over 50% of all nosocomial infections. Third, the rise of MDR pathogens possesses a global problem, and prevention of these must not be omitted.[7]

I have mentioned the basic preventive measures and guidelines provided by CDC (USA), WHO (international) or Fhi (Norway), which are the mainstay for preventing infections. A report from the WHO showed that the hands of health-care workers are the most common routes for transmission of pathogens to patients. Thus this is the leading preventive measure, yet the area with lowest practice and compliance. [1] To change this there was conducted a study that compared normal hand washing with the use of disinfectant. The study showed that the use of disinfectant, not only had better antimicrobial efficacy, but it also increased compliance among healthcare workers. Compliance was improved by training and by placing the dispenser at easily accessible places. The study concluded that this could help reduce nosocomial infection rate by 40%. [17]

Other measures to encourage hand hygiene should also be focused on. The American Journal article describes a hospital-staff driven campaign, which ended in success. The campaign included education about hand hygiene, slogans and rewards for the winning ward. This created increased awareness of hospital staff and resulted in a rise in compliance from 34% to 80% with in one year. [26]

A further topic for discussion is infections due to invasive devices. The application of medical device is almost an indispensable part of medicine nowadays. But the insertion of foreign bodies in patients is not without risks. Hence, implant-associated infections are a significantly contribution to nosocomial infections. To reduce this there are developed specific preventive strategies. They include the basic measures with strict adherence to hygiene and asepsis during handling of devices and insurance of atraumatic insertion. Besides this, research on new materials that can withstand microbial adherence and colonisation, has been tried. The material is modified in such a way that microbes would not be able to adhere and thus a following infection will be unlikely. However it appears impossible to create such a material with zero adherence. Therefore, the concept of impregnation of device and catheters with antibiotic, antiseptics and/or metals were proposed. This has been with variable success in preventing disease.[5,34] There was conducted a study in 2005, to assess the clinical and cost effectiveness of antiseptic coated catheters for critical ill patients. The method included the coating of CVC with chlorhexidine/silver-sulfadiazene in an ICU in USA. The result showed a 4% per month relative decrease in the incidence of CRBI. Also the use of antiseptic catheters reduced costs with over $100,000 annually. The use of Vancomycin was in addition reduced in units with coated catheters, compared to those wards without. They concluded that antiseptic-coated catheters appeared to be both clinically and cost effective. [6]

In USA they have tried another strategy to prevent CRBI. They hired specialised nurses who are trained to handle catheters (CVC) correctly. This has proven to be very effective in preventing CRBI. This could be a strategy useful to adopt, especially on wards with high-risk patients (ICU).

An area of future interest and concern is the development of resistant bacteria. It has been a problem since the usage of antibiotics exploded during late 1970's.
MDR bacteria are occurring in all hospitals and wards, but it is especially a problem in ICU. Here patients are already severely ill and the development of an infection can be disastrous. In addition physician seldom know the causative agent and thus need to

administer broad-spectrum antibiotics, which is a major risk factor for emergence of MDR pathogens. There are guidelines and recommendations that aiming for correct antibiotic treatment and prophylaxis, but it is not always correctly adhered to. The WHO states that the incorrect administration and use of antibiotics are the main cause of emergence of resistant bacteria.[7]

There exist strategies aimed at reducing infections with MDR pathogens. Some of these include isolation of patient with proved infection, pre-emptive isolation of high-risk patients and active surveillance culture (ASC).[18] Guidelines for preventive strategies varies between countries.

An example is Norway, which has a low occurrence of MRSA. The key point in their strategy is screening of persons who are at risk for having MRSA. Risk persons include patients and workers who have had MRSA before, lived together or had intimate contact with other persons with MRSA or persons who have been outside of Norway the last 12 months or who have stayed in a country outside of Scandinavia for over 6 weeks. In addition all persons who have clinical symptoms on skin are recommended for testing. [10] The screening will detect any MRSA positive individuals before admission. This will reduce the time that the colonised patient comes in contact with staff or other patients and hence prevent transmission. These rigours prevention programs are shown to be effective. The prevalence in Scandinavian countries and in the Netherlands is still at a low level < 1-3%. Another method proven to work is the detection of MRSA with PCR instead of culture. This gives a rapid detection (within 2-5 hours) of carriers and is very effective to prevent transmission. There may be false positive results with PCR, but these are ruled out with taking culture simultaneously. This data provide evidence that PCR can reduce nosocomial MRSA transmission in high-risk patients or in risky areas. However, it will not be cost-effective to screen all hospital-admitted patients. [32]

International guidelines recommend that only ICU should use ASC. These microbiological cultures have also been suggested to decrease the number of MRSA, but it has not been proven. A study concluded that it still exist important gaps in the literature to be sure of its effect, but that existing evidence may favour its use. Although no definite recommendation can be made. [24]

Other strategies, such as vaccines aim at reducing the antibiotic use and thus to prevent the occurrence of MDR pathogens. The pneumococcal vaccine was included in the child vaccination program in Norway (2006). It has been administered in the

USA since 2000, and proven to effectively reduce infections with Streptococci pneumonia. There was also found a reduction of 42% in prescribing antibiotics for acute otitis media. Pre-school children are the main reservoir and thus vaccination will give a better immunity against pneumococci in the community. [14]

The vaccination against Influenza has also proven to be effective. Influenza increases the risk for secondary bacterial pneumonia, hospitalisation and antibiotic administration. A study showed that 38% of patients in USA got antibiotics for respiratory symptoms, when there was no bacterial infection. The vaccine also protects older and immunocompromised patients towards hospitalisation, where they are at risk for nosocomial infections. Thus the vaccine is especially indicated for this group of patients.[14] This documentation proves that vaccines can reduce the administration of antibiotics, and thus decrease the emergence of MDR pathogens.

Further development of new microbial agents is also important for the future handling of infections. But new drugs are expensive and the development is time consuming. There has also been noticed a decrease in the research-based pharmaceuticals industry when it comes to infectious diseases. Instead this interest has turned towards development of lifestyle drugs. If this trend doesn't change, the likelihood that effective therapies for some pathogens will be absent during next ten years is quite certain. [36]

5. Conclusion:

My paper is written with the main focus on how to prevent the most frequent infections and the development of MDR pathogens. During my literature search I found various studies showing the importance of preventive measures. They reduce morbidity, mortality and costs.

All hospital should have an infection-control program, which must include information, education, guidelines and recommendations for personal hygiene, antibiotic treatment and handling of outbreaks in hospitals. These programs have shown to be very effective in decreasing the occurrence of infections.

People are the centre of the phenomenon of nosocomial infection. They are the main source of microorganisms and the main ”vehicle” for transmission. This makes hand hygiene the single most important preventive measure. Thus it must be encouraged and hospital workers must be educated and reminded about this topic.

Due to the increasing use of invasive medical devices, this must be an area with further improvement. The research done show that infection rate can be reduced if device were coated with antiseptic solutions. The infection rate was also decreased when special educated nurses were responsible for the manipulation of catheters. This could be incorporated in units experiencing high occurrence of nosocomial infections and where these infections are harder to treat, leading to increased morbidity and mortality (ICU).

ICU is also a site where MDR pathogens are found more frequently compared to other wards. This is due to the frequent use of broad-spectrum antibiotics.

There exist antibiotic policies and control programs, but they are not always adhered to, and thus incorrectly administered, leading to the emergence of resistant pathogens.

Some countries (Scandinavia and the Netherlands) have proven to be successful in preventing the rise of MRSA in hospitals. Thus these measures and strategies may be introduced elsewhere with the same positive effect. Furthermore, should the focus be kept on measures that can contribute to the reduction in antibiotica administration (such as new vaccines).

Raising awareness of the problem, sharing of information, stimulate research to address knowledge gaps and to improve understanding of resistance and to further encourage the development of new antimicrobial agents are important for the future.

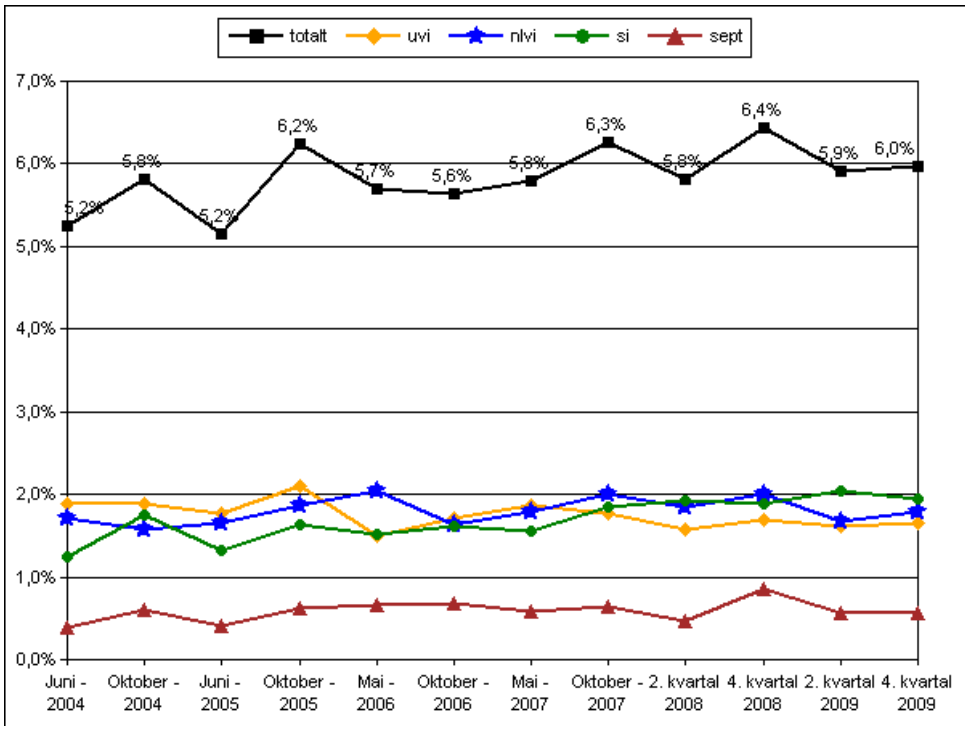
Antibiotic resistance is a global area of concern, which demands a global response now.

Appendix 1

In Norway, Folkehelseinstituttet (public-health institute) is responsible for the documentation and reporting of hospital-acquired infections.

It has since 2002 done annual reports on the prevalence of nosocomial infections.

The result from the spring survey (2009) showed a prevalence of 5,9% of infections occurring in hospital settings.



The table shows the prevalence of nosocomial infections in Norway from 2004-2009.

9

Bibliography:

1. Allegranzi B et al. “Role of hand-hygiene in healthcare-associated infection prevention” The journal of hospital infection, Aug 2009. http://www.ncbi.nlm.nih.gov/pubmed/19720430

2. Bert F, Lambert-Zechovsky N, “Sinusitis in mechanically ventilated patients and its role in the pathogenesis of nosocomial pneumonia.” European journal of clinical microbiology and infectious diseases, Jul 1996 http://www.ncbi.nlm.nih.gov/pubmed/8874069

3. Burkitt H. George, et al, “Essential surgery, problems, diagnosis and management”, Churchill Livingstone Elsevier, 2007 p.144.149

4. Center for disease control (CDC) http://www.cdc.gov/ncidod/dhqp/id.html

5. Darouiche “Antimicrobial coating of device for prevention of infection” International journal of artificial organs, Sept 2007http://www.ncbi.nlm.nih.gov/pubmed/17918128

6. Debaroti, M. Borschell et al “Are antiseptic-coated CVC effective in a real world setting?” American journal of infection control, Dec 2005

7. Ducel, G. et al “Prevention of hospital-acquired infections- a practical guide” WHO, 2002. http://www.who.int/emc

8. Dzupova, O. MUDr. Lecture “Nosocomial infections” Bulovka hospital, Oct 2008.

9. Folkeheslseinstituttet i Norge http://www.fhi.no/

10. Folkehelseinstituttets “Smittevern 16, MRSA veileder” Jun 2009

11. Fumagalli R, and Groeneveld AB, J “Pyrexia clinical problem” PACT, March 2005 http://pact.esicm.org/main/newscorm/lp_controller.php?action=view&item_id=21#rubrique_21

12. Haley Robert W, et al “The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals” American journal of epidemiology 1985. http://aje.oxfordjournals.org/cgi/content/short/121/2/182

13. Harnoz Julian-Camill, et al “Concentration of bacteria passing through puncture holes in surgical gloves” American journal of infection control, Oct 2009 http://www.ajicjournal.org/article/S0196-6553(09)00754-8/abstract

14. Harthug, S and Akselsen, P.E “Tiltak mot antibiotikaresistens”, Tidsskriftet for den norske legeforening, Oct 2008. http://www.tidsskriftet.no/index.php?seks_id=1750859

15. Historylearningsite.co.uk/alexander_fleming_and_penicillin.htm

16. Hobstova, J and Coll “Infections diseases” Charles university in Prague, 2003 p.138-143

17. Kampf G et al. “Hand-hygiene for the prevention of nosocomial infections”, Dtsch Arztebl Int oct 2009 http://www.ncbi.nlm.nih.gov/pubmed/19890431

18. Kitson, R et al “Infection control strategies” PACT, 2010 http://pact.esicm.org/main/newscorm/lp_controller.php

19. Lopman BA, Adak GK, Reacher MH, Brown DWG. Two epidemiological patterns of *Norovirus* outbreaks: surveillance in England and Wales, 1992-2000. Emerg Infect Dis, 2003 http://www.cdc.gov/ncidod/EID/vol9no1/02-0175.htm

20. Nicolle, L.E “Nosocomial infection” http://www.healthline.com/galecontent/nosocomial-infections

21. Mangiadi, J.R, MD FACS and Ray Marcovici “History of hospital acquired infections”, 2007 http://www.optimusise.com/history-hospital-infection.php

22. Macintyre NR and Rubin BK “Respiratory therapies in the critical care setting. Should aerosolised antibiotics be administered to prevent or treat ventilator-associated pneumonia in patients who do not have cystic fibrosis?” Respiratory Care Services, Duke University Medical Center, USA, April 2007. http://www.ncbi.nlm.nih.gov/pubmed/17417976

23. Marshall, J.C et al “Clinical problems, sepsis and MODS” PACT (patient-centred acute care training), 2008 s. 1-5

24. McGinigle KL, Gourlay ML, Buchanan IB “The use of active surveillance cultures in adult intensive care units to reduce methicillin-resistant Staphylococcus aureus-related morbidity, mortality, and costs: a systematic review.” Clinical infectious diseases, Jun 2008. http://www.ncbi.nlm.nih.gov/pubmed/18494098

25. Merck Manuals medical library; Sepsis and septic shock http://www.merck.com/mmpe/sec06/ch068/ch068a.html?qt=sepsis&alt=sh

26. Micklow, K. et al “Hand hygiene: staff-driven approach leads to success”, American journal of infection of control, june 2006. http://www.ajicjournal.org/article/S0196-6553(06)00642-0/abstract

27. Murray Patrick, Phd et al “Medical microbiology” Elsevier Mosby, 2005 p.850

28. Pruss, A. et al “Safe management of waste from health- care activities” The WHO, Geneva 1999 p. 154-156

29. Reproline.jhu.edu/english/4morerh/4ip/IP_manual/20_Nosocomial.pdf.

30. Shojamanesh, Homayoun MD “Acalculous cholecystitis” Emedicine 2007 http://emedicine.medscape.com/article/187645-overview

31. Stedman’s concise medical dictionary

32. Sturenburg E, “Rapid detection of methicillin-resistant Staphylococcus aureus directly from clinical samples: methods, effectiveness and cost considerations.” Ger Med Sci, Jul 2009. www.ncbi.nlm.nih.gov/pubmed/19675746

33. Toni Rizzo "Hospital-acquired infections". Encyclopedia of Medicine. FindArticles.com. 18 Mar, 2010. http://findarticles.com/p/articles/mi_g2601/is_0006/ai_2601000684/

34. Von Eiff c et al ”Modern strategies in the prevention of implant associated infection” International journal of artificial bodies, nov 2005. http://www.ncbi.nlm.nih.gov/pubmed/16353121

35. Weinstein Robert, ”Nosocomial infection update” Emerging infectious diseases, volume 4, number 3, 1998. http://www.cdc.gov/ncidod/eid/vol4no3/weinstein.htm

36. WHO ”WHO global strategy for containment of antimicrobial resistance”, 2001 http://whqlibdoc.who.int/hq/2001/WHO_CDS_CSR_DRS_2001.2.pdf

37. Wikipedia.org/wiki/Hospital_Acquired_Infections

38. Wrongdiagnosis.com/mistakes/nosocomial.htm (medical article)