VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Nosocomial pneumonia

Pneumonia is an inflammatory condition of the lungs. Nosocomial pneumonia describes hospital-acquired pneumonia (HAP), health care-associated pneumonia (HCAP), or ventilator-associated pneumonia (VAP); all of which are delineated primarily based on the time of onset and etiology of infection (Hooper and Smith, 2012). Nosocomial infections include infections that happen in hospital and were not present at time of admission, and infections acquired in hospital that become apparent within seven days following hospital discharge. Ventilator-associated pneumonia (VAP) is the second most frequent hospital-acquired infection and one of the most aggressive; it is often associated with higher rates of complications and death, as well as with increased hospital stays and costs. VAP constitutes 80% of nosocomial pneumonia, occurring in approximately 10% to 20% of patients requiring mechanical ventilation for more than 48 hours, with case fatality between 24% and 76%. (Mendell et al., 2013).

Broncho-pulmonary infections in cystic fibrosis

Cystic fibrosis (CF) is a common genetic disease whose major clinical manifestations include repeated episodes of airway infection and inflammation that ultimately result in early death from respiratory failure (Leclair and Hogan, 2010). The main cause of complications and death in patients with cystic fibrosis (CF) is chronic lung infection with *Pseudomonas aeruginosa*. Other respiratory pathogens play a role at different stages of the lung disease of CF patients, such as *Staphylococcus aureus* and *Haemophilus influenzae* in infants and children and *Burkholderia cepacia* complex, *Achromobacter xylosoxidans, Stenotrophomonas maltophilia* and nontuberculous mycobacteria (NTM) in adults (Ciofu et al., 2013).

Bacterial meningitis

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. Meningitis refers to a group of infectious diseases of great social relevance, particularly taking into account the high fatality rates and consequential damages that may occur when the membranes that envelop the brain are invaded by certain microorganisms. These diseases are included in the top 10 causes of death by infectious diseases worldwide, especially in developing countries (De Souza et al., 2012).

Although the incidence and rates of complications and death from acute meningitis have dramatically declined, probably as a result of vaccination and better antimicrobial and adjuvant therapy, the disease still has a high toll. From 10-20% of people who contract it in the United States still die of it. The organisms that cause community-acquired bacterial meningitis differ somewhat by geographic region and by age (Bhimraj, 2012).

Chronic suppurative otitis media

Otitis media is the medical term for middle ear infection. Chronic suppurative otitis media involves a perforation (hole) in the tympanic membrane and active bacterial infection within the middle ear space for several weeks or more. Chronic Suppurative Otitis Media (CSOM) is typically a persistent disease, insidious in onset, often capable of causing severe destruction and irreversible damage and clinically manifests with deafness and discharge. This is one of the most common community health disorders of childhood in many developing countries. Its incidence appears to depend to some extent on race and socioeconomic factors. High rates of chronic otitis media have been attributed to overcrowding, inadequate housing, poor hygiene, lack of breast feeding, poor nutrition, impaired immunologic status, passive smoking, frequent upper respiratory tract infection, high rates of nasopharyngeal colonization with potentially pathogenic bacteria and inadequate or unavailable health care (Shaheen et al., 2012).

Malignant otitis externa

Otitis externa is an inflammation of the outer ear and ear canal. Necrotizing external otitis (malignant otitis externa) is an uncommon form of external otitis. It can develop due to a severely compromised immune system. Beginning as infection of the external ear canal, there is extension of infection into the bony ear canal and the soft tissues deep to the bony canal. The hallmark of malignant otitis externa (MOE) is unrelenting pain that interferes with sleep and persists even after swelling of the external ear canal may have resolved with antibiotic treatment on the surface (Saxby et al., 2010). Malignant external otitis (MEO) is a severe disease whose diagnosis and treatment is a challenge for any specialist. MEO occurs in patients with decreased immune systems mostly elderly diabetics (90%), generally insulin-dependent and poorly controlled. There are also forms of MEO in youths and children. Although mortality was high for the past few years, at present the prognosis has improved (Pérez et al., 2010). MEO is a life threatening, progressive bacterial infection of the external auditory canal (EAC), mastoid and skull base. In nearly all cases *Pseudomonas aerugenosia* is the causative organism (Bains and Dhooria, 2010).

Complicated urinary tract infections

The urinary tract is the most common site of bacterial infections. Urinary tract infections in women require frequent and repeated use of drugs that kill bacteria, which can lead to resistant bacteria (Carraro-Eduardo and Gava, 2012).
Urinary tract infection is one of the most common bacterial infections seen at the family doctor´s practice. Infections of the urinary tract can present with various symptoms and signs and are particularly common among women, with an incidence of about 3-9% in young women and 20% in women aged more than 65 years (Medina-Bombardo and Jover-Palmer, 2011). Urinary tract infections can spread to the blood and cause bacteraemia (Beveridge et al., 2011).

Complicated skin and soft tissue infections

Skin and soft tissue infections are versatile and associated with complications. They often require hospitalisation. Such infections often require surgical procedures (in addition to therapy with an antibiotic) and can involve deeper tissues (e.g. conjunctive tissue or muscles). Skin and soft tissue infections are now more challenging to manage, as the spectrum of bacteria that

cause the infection is more complex and some microorganisms have developed resistance to antibiotics (Lipsky et al., 2012).
Skin and soft tissue infections are a common reason for presentation to outpatient practices, emergency rooms, and hospitals. They account for more than 14 million outpatient visits in the United States each year, and visits to the emergency room and admissions to the hospital for them are increasing (Rajan, 2012).

Complicated intra-abdominal infections

Intra-abdominal infections are infections of the body cavity below diaphragm that contains stomach, intestines, liver and other organs. Intra-abdominal infections represent a particular clinical challenge, as they differ from other types of infections in a number of aspects. The clinical spectrum of intra-abdominal infections is very broad, ranging from uncomplicated inflammation of the blind gut to generalised inflammation of the belly fur (Blot et al., 2012).
Antimicrobial therapy plays an important role in the management of intra-abdominal infections, especially in patients who are treated in the intensive care unit and who require immediate antibiotic therapy. An insufficient or otherwise inadequate antimicrobial treatment is most strongly associated with unfavourable outcomes (Sartelli et al., 2012).
The main objective of antimicrobial therapy in the treatment of intra-abdominal infections is a prevention of a local spread or of a spread to the blood, and to reduce late complications. As for other infections, early administration of antibacterials is important (Blot et al., 2012).

Bone and joint infections
Examples for bone and joint infections are osteomyelitis or septic arthritis. In the past, osteomyelitis infections were mainly the results of direct bacterial penetration into the bone or adjacent tissues, through soft tissue lesions secondary to low-energy traumas (wounds, falls, punctures, bites, etc.) or to hematogenous spreading of the microorganisms from inflamed areas localised in other organs and apparatus. While those mechanisms of bacterial colonisation of the bone tissue have not disappeared, especially in the industrialized world and during the last century, a progressive increase of bone and joint infections due to high-energy traumas (wars, traffic, sports, etc.) or secondary to surgical procedures has been observed. Besides this, more and more osteomyelitis and septic arthritis today are found to be causally related with dismetabolisms (diabetes, renal insufficiency, etc.), diseases of the vessels and nerves, life habits (smoking, drug, or alcohol abuse), inherited or acquired deficiencies of the immune system, and advanced age (Romanó et al., 2011).

Peritonitis associated with dialysis in patients on CAPD.

Continuous ambulatory peritoneal dialysis (CAPD) has become the preferred method of home dialysis for patients with end-stage renal failure. An inflammation of the belly fur (peritonitis) is a common and serious complication and requires prompt diagnosis and treatment. Peritonitis is the second commonest cause of death in patients undergoing CAPD (Al-Allak et al., 2009). Patients treated with peritoneal dialysis are exposed to a possible infection of the peritoneal cavity due to the non-natural communication of the peritoneal cavity with the exterior of the body through the dialysis catheter, and the repeated introduction of the dialysis fluid into the peritoneal cavity. The dialysis procedure itself is therefore a risk for a belly fur infection (Montenegro et al., 2007).

Bacteraemia

Bacteraemia is the presence of bacteria in the blood. Bacteraemia is a serious infection which is associated with many complications and death. Gram-negative bacteria have been documented as the most common cause of bacteraemia in many countries, but also infections caused by other bacteria represent an emerging problem in clinics, especially in patients with a depressed immune system. The bacteria that can cause bacteraemia are very problematic because of their

ever-present distributions in the environment and their antimicrobial resistance patterns (Rattanaumpawan et al., 2013).
In high-income countries, the rate of hospitalisation due to bacteraemia is around 77 to 92 per 100,000 people per year, and 13 to 19% die after 30 days. Bacteraemia is now the eleventh most frequent cause of death in the United States (Kanoksil et al., 2012).

Neutropenic patients with fever

Febrile neutropenia is the development of fever, often with other signs of infection, in a patient with neutropenia, an abnormally low number of neutrophil granulocytes (a type of white blood cell) in the blood (Cooper et al., 2011). Febrile neutropenia is still associated with many deaths, making timely and efficient empirical antibiotic therapy absolutely vital (Glasmacher et al., 2005).
Febrile neutropenia is associated with complications, deaths, and costs. The direct risk of death associated with febrile neutropenia has been estimated as 9.5% in a study of 41.779 cancer patients hospitalised with febrile neutropenia (Cooper et al., 2011).
Febrile neutropenia presents a clinical challenge in which timely and appropriate antibiotic treatment is crucial. Antibiotic treatment in febrile neutropenia is becoming increasingly difficult due to a rising antibiotic resistance. Alternative dosing strategies, such as extended or continuous infusions of beta-lactam antibiotics, to maximise the likelihood of treatment success, have been developed (Abbott and Roberts, 2012).

Peri-operative prophylaxis of urinary tract infections after transurethral resection of the prostate

Transurethral resection of the prostate (TURP) is accepted as the gold-standard surgical treatment of benign prostatic hyperplasia (an increase in number of cells, which may result in the gross enlargement of an organ and lead to cancer) which is a common condition in the aging male. Postoperative bacteriuria is a common event after TURP and is seen in 1.8–64% of the patients. The death related to postoperative bacteriuria due to the development of septic shock arising from the urinary tract is seen in about 0.1% of the patients with a preoperative sterile urine. The development of urinary tract infections causes longer hospital stay and increases the cost of the operation. Appropriate antibiotic prophylaxis will prevent septicemia in almost all cases (Ozturk et al., 2007).

VI.2.2 Summary of treatment benefits

- ***Nosocomial pneumonia***

  Bassetti et al. (1998) treated 72 patients with nosocomial pneumonia or bacteraemia with ceftazidime. 90% of the patients were cured.

- ***Broncho-pulmonary infections in cystic fibrosis***

  The efficacy of ceftazidime in the treatment of infections of the airways in patients with cystic fibrosis has been evaluated in several studies (Norrby, 1983; Strandvik et al., 1983; Kercsmar et al., 1983; Mastella et al., 1983; Permin et al., 1983; Dodge et al., 1983). All studies describe ceftazidime as an effective treatment of patients with cystic fibrosis and infections of the airways, especially caused by *Pseudomonas aeruginosa*.

- ***Bacterial meningitis***

  Hatch et al. (1986), Rodriguez et al. (1985) and Rodriguez et al. (1986) described ceftazidime as an effective monotherapy for the treatment of bacterial meningitis and as favourable over the standard therapy with chloramphenicol plus ampicillin.

- ***Chronic suppurative otitis media***

  Somekh and Corodva (2000) treated 15 children with chronic suppurative otitis media with ceftazidime. Success rate, definded as complete disappearance of discharge, was 84.6% with ceftazidime (compared to 67% in patients treated with aztreonam).

- ***Malignant otitis externa***

  Loh and Loh (2013) summarised several studies on the treatment of malignant otitis externa and they recommend the combination of intravenous ceftazidime with oral fluoroquinolone for the treatment of malignant otitis externa.

- ***Complicated urinary tract infections***

  Cure rates of at least 85% have been reported during treatment of complicated urinary tract infections with ceftazidime (Naber et al., 1983; Cox, 1983; Cox, 1993; Rapp et al., 1991, Vozza et al., 1990).

- ***Complicated skin and soft tissue infections***

  Noel et al. (2008) used ceftazidime in combination with vancomycin for the treatment of complicated skin and soft tissue infections. They achieved clinical cure rates of 90.2%.

- ***Complicated intra-abdominal infections***

  Angeli (2006) used intravenous ceftazidime for the treatment of bacterial peritonitis. Resolution of infection was achieved in 84% of the patients.

- ***Bone and joint infections***

  Gentry (1985) and Dutoy et al., 1983 used ceftazidime for the treatment of bone and joint infections. Overall cure rates were 75% and 85%, respectively.

- ***Peritonitis associated with dialysis in patients on CAPD***

  Ceftazidime was used in several studies for the treatment of peritonitis associated with dialysis in patients on CAPD either as monotherapy or in combination with other antibiotics (Lui et al., 2005; Guček et al., 1997; Keane et al., 1993, Schaefer et al., 1999; Leung et al., 2004). Cure rates were above 80% in all studies.

- ***Bacteraemia***

  Kieft et al (1993) and Norrby et al. (1998) both reported cure rates of 86% when bacteraemia was treated with ceftazidime.

- ***Febrile neutropenia***

  Çorapçıoğlu and Sarper (2005) used ceftazidime in combination with amikacin to treat febrile neutropenia. The authors describe ceftazidime in combination with amikacin as an effective treatment of pediatric cancer patients with febrile neutropenia.

- ***Peri-operative prophylaxis of urinary tract infections for patients undergoing transurethral resection of the prostate (TURP)***

  Ozturk et al. (2007) evaluated the risk of bacteriuria after TURP and the preventive effects of different kinds of antibiotics. Ceftazidime treatment prevented urinary tract infection in 93.2% of the patients.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions to ceftazidime, sodium, other cephalosporins or any other type of beta-lactam antibiotic. (Hypersensitivity to the active substance ceftazidime, to any other cephalosporin or to any of the excipients and/or a history of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam agents (penicillins, monobactams or carbapenems).)	As with all beta-lactam antibacterial agents, serious and occasionally fatal allergic reactions have been reported. In case of severe allergic reactions, treatment with ceftazidime must be stopped immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe allergic reactions to ceftazidime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if ceftazidime is given to patients with a history of non-severe allergic reactions to other beta-lactam agents. The following serious side effects have occurred in a small number of people but their exact frequency is unknown: - Severe allergic reaction. Signs include raised and itchy rash, swelling, sometimes of the face or mouth causing difficulty in breathing. - Skin rash, which may blister, and looks like small targets (central dark spot surrounded by a paler	Yes, by monitoring for early symptoms and by carefully studying the patient´s medical history.

Risk	What is known	Preventability
	area, with a dark ring around the edge). - A widespread rash with blisters and peeling skin. (these may be signs of *Stevens-Johnson syndrome* or *toxic epidermal necrolysis*).	
Severe persistent diarrhoea due to infection of the bowel with bacteria during or after treatment with ceftazidime (Antibacterial agent-associated colitis and pseudomembraneous colitis.)	A rare but possibly life-threatening side effect of ceftazidime is the occurrence of severe persistent diarrhoea due to an infection of the bowel with certain bacteria during or after treatment with ceftazidime. Tell your doctor if you experience severe diarrhoea during or after treatment. This may affect up to one in 100 people.	Yes, by carefully monitoring for early symptoms.
Increased risk for kidney toxicity during intake of high doses of cephalosporins or simultaneous intake of diuretics or antibacterials which belong to the group of aminoglycosides (medicinal products with the ending -mycin or -micin). (Increased risk for renal toxicity during concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics.)	Simultaneous treatment with high doses of cephalosporins and medicinal products, which can be toxic to the kidneys, such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect kidney function.	Yes, by carefully monitoring for early symptoms.
Patients with impaired kidney function (e.g. elderly patients) are at risk for toxicity and severe adverse reactions. (Increased risk for toxicity and severe adverse reactions in patients with renal impairment.)	Nervous system disorders, such as tremors, fits and, in some cases coma have occurred in people when the dose they are given is too high, particularly in people with kidney disease.	Yes, by carefully monitoring the renal function of the patient and by monitoring for early symptoms.
Infection with microorganisms that are not susceptible to ceftazidime.	It is possible, that certain bacteria or fungi are not eradicated by ceftazidime and they can cause a so called	Yes, by carefully monitoring the patient.

Risk	What is known	Preventability
(Overgrowth of non-susceptible microorganisms).	"superinfection". This can lead to thrush - fungal infection of the mouth or the vagina. This may affect up to one in 100 people.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use of ceftazidime during pregnancy	There are limited amounts of data from the use of ceftazidime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Due to the lack of data, the use of ceftazidime during pregnancy is considered to be a potential risk. Tell your doctor before you are given ceftazidime: - if you are pregnant, think you might be pregnant or are planning to become pregnant - if you are breastfeeding Your doctor will consider the benefit of treating you with Ceftazidim MIP against the risk to your baby.

Important missing information

Ceftazidime is a medicinal product of well-established use in humans and, therefore, no information is missing.

Risk	What is known
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VI.2.5 Summary of risk minimisation measures by safety concern

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.