

EXTENDED-SPECTRUM BETA-LACTAMASE RESISTANCE

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Beta-lactamases are enzymes produced by bacteria that breakdown (and thus inactivate) a particular class of antibiotics called the beta-lactams. The first antibiotic was discovered by Sir Alexander Fleming in 1927 and was named penicillin, which is a beta-lactam. It was not until the early 1940s, through the work of Drs. Florey, Chain and Heatley from Oxford University, that penicillin was purified and shown to cure specific bacterial infections. Since that time, many chemical derivatives have been developed from penicillin to combat resistance that has arisen in bacteria. These derivatives commonly referred to as the extended-spectrum beta-lactams, include antibiotics called the cephalosporins, carbapenems and monobactams. Over the last 60 years, the beta-lactam class of antibiotics were the most widely used, and represent about 60% of all of the antibiotics used (by weight) in human and animal medicine. This is primarily because in general they work well against bacteria and are safe for human and animal consumption with few side effects observed.

How do the beta-lactam antibiotics kill bacteria? These antibiotics stop the synthesis of the bacterial cell wall. As the contents inside a bacterial cell are much different from the outside environment, a wall needs to be produced which provides structure and prevents the cell from bursting like a

balloon. The beta-lactam antibiotics bind to the components that build this wall and inactivate them. Thus, bacteria can no longer produce the cell wall and they burst and die. To counteract the effects of the beta-lactam antibiotics the bacteria have evolved enzymes called the beta-lactamases which break down the beta-lactam drugs. Thus they are capable producing the cell wall even in the presence of the beta-lactam drugs and are classified as resistant.

As the bacteria developed resistance to one type of beta-lactam antibiotic, new antibiotic derivatives were made by researchers and were called the cephalosporins, carbapenems and monobactams, but the bacteria continually evolved and changed existing beta-lactamase enzymes to break down these new compounds. The enzymes that can break down the newer derivatives are known as the extended-spectrum beta-lactamases (ESBLs) and were first observed in the early 1980's.

ESBLs can be found in many different types of bacteria and thus infections caused by ESBLs producing bacteria are numerous. Infections can involve the respiratory tract (pneumonia), urinary tract and bladder, skin and soft tissue, blood, gastrointestinal tract, reproductive organs, and central nervous system. Generally speaking, individuals with infections caused by bacteria carrying ESBLs have a higher mortality rate and require longer stays in hospitals,



thus increasing the costs of patient care. Although a large number of studies have examined risk factors associated with ESBLs related infections the data in some regards is conflicting. This may be the result of study design, types of ESBLs observed, or the types of bacteria that carry ESBLs. However, general risk factors can be extrapolated from these studies. Patients are often seriously ill with prolonged hospital stay. Patients that have indwelling medical devices such as urinary catheters, breathing devices, or intravenous lines in major veins in the neck, groin or chest are at higher risk for infections caused by ESBL strains. These devices are usually inserted for a prolonged duration. In addition, individual studies have also shown risk factors which include the presence of various stomach tubes, arterial lines, administration of total nutrition intravenously, or heavy use of antibiotics within six months. Other risk factors such as individuals with recent surgery, hemodialysis, bed sores, and poor nutritional status also have a higher risk of obtaining an infection with a bacteria producing an ESBL. These risk factors occur in the hospital setting, but are also common in long term care facilities or nursing homes.

Generally, ESBLs are not carried on the bacterial chromosome, rather they are found on an independent element of DNA called a plasmid. Plasmids can carry many different genes on them and have the ability to transfer a replica of themselves to other bacteria. This can be very serious for a

number of reasons. Firstly, the “other” genes could include genes conferring resistance to other classes of antibiotics that make the recipient bacteria resistant to multiple antibiotics or what is sometimes reported in the press as a “Superbug”. Also, these plasmids can emerge in strains that do not cause human disease, but then the non-pathogenic strains could transfer their plasmids to strains that can cause human disease. Much research is being conducted into the association of bacteria identified in animals and the environment and the potential linkage of antibiotic resistant human disease causing bacteria. Antibiotics are used in the food animal industry not only to treat infections, but also to prevent them and also to enhance growth.

Since beta-lactam antibiotics are commonly prescribed for infections caused by these organisms prior to the knowledge that the bacteria is resistant, it is necessary for a physician to switch the patient to a different antibiotic when the laboratory identifies an ESBL carrying bacteria. However, since these organisms are in many cases resistant to multiple antibiotics (see above), the physician is limited to his choice for antibiotics. One of the treatments of choice for individuals infected with ESBLs is the use of the relatively new beta-lactam derivative group called the carbapenems. Unfortunately, we are beginning to see resistance to this type of antibiotic as well, although it is still rare in Canada.

To conclude, bacterial resistance to this class of antibiotic



highlights the struggle between new drug development and the evolution of resistance in bacteria. Whenever a new modified beta-lactam compound is developed that shows activity against bacterial infections, the bacteria fight back and evolve new enzymes to inactivate the new compound. Increased surveillance is necessary to monitor this type of resistance not only in bacteria that cause human disease, but also in bacteria from animal and environmental sources. This will help identify the sources of this type of resistance and lead to potential corrective measures. Continued research is required to develop novel derivatives of this highly successful antibacterial compound and keep one step ahead of the resistant strains.

Selected Reading

1. Livermore DM, Woodford N. The beta-lactamase threat in Enterobacteriaceae, Pseudomonas and Acinetobacter. *Trends Microbiol.* 2006 Sep;14(9):413-20. Epub 2006 Jul 31.
2. Ramphal R, Ambrose PG. Extended-spectrum beta-lactamases and clinical outcomes: current data. *Clin Infect Dis.* 2006 Apr 15;42 Suppl 4:S164-72.
3. Pfaller MA, Segreti J. Overview of the epidemiological profile and laboratory detection of extended-spectrum beta-lactamases. *Clin Infect Dis.* 2006 Apr 15;42 Suppl 4:S153-63.

