Bacterial resistance to new and existing antibiotics is a well-documented problem and despite higher standards than ever in intensive care wards across the developed world, it is generally expected that it will evoke an increase in severe infectious diseases and lead to mortality rates that will not significantly decline in the near future.

Serious complications in infectious diseases such as sepsis constitute a life-threatening medical condition characterised by a whole-body inflammatory state, and usually referred to in layman’s terms as blood poisoning.

The symptoms are a culmination of complex interactions between the infecting microorganism and host immune responses. Such findings have prompted several research groups, including one led by Dr Heiko Herwald, at the Lund University in Sweden, to search for strategies to treat such infections. Many of these approaches are focused on ‘host effector systems’ (HES) since there is evidence that complications from an infection are caused by an over-stimulation of host defence systems that had been modulated by bacteria or bacterial products.

“One reason for a high mortality rate is that the population is getting older and the immune system of elderly people is not functioning the way it should be,” said Dr Herwald.

“We have more and more diseases which require suppression of the immune system, for example in cancer, where the immune system has been knocked out.

“Then there is resistance to antibiotics. If one combines all these different aspects it can be predicted that the number of severe infectious diseases will increase when at the same time more bacterial pathogens will become resistant to antibiotics. These prospects will pose a major clinical challenge for physicians and researchers.

“If a new antibiotic is administered to patients, there is a risk that within five to 10 years bacteria develop mechanisms that make them resistant. This phenomenon has been known for a long time. For instance penicillin resistance in Staphylococcus aureus was reported as early as 1947, even though it was introduced into hospitals only five years before. Today many important pathogens are even multi-resistant and in some cases patients do not respond to an antibiotic treatment at all. There is therefore an urgent need for novel antimicrobial therapies with a completely different mode of action. So if one looks at the patients who become really ill, what

Heiko Herwald has been researching new and novel antimicrobial therapies for treating bacterial infection for 10 years and his work is having real impact on the treatment of life-threatening complications that are the second leading cause of death among patients in non-coronary intensive care units in Europe.
happens is that they are not only diseased because of the pathogen, it is also because patients overreact to infection. This is because of host effective systems and due to their evoking pathological conditions. What we do is to study host-pathogen interaction with the aim of identifying HES that are over-stimulated and able to trigger severe complications. And once we have identified this we would like to modify it with synthetic inhibitors in order to dampen the response to infection and also to develop new drug targets.”

The project, which has been running for a decade, has focused particularly on the human contact system, which has shown to become over-activated by bacteria and can cause sudden onset of serious disease. The Lund group has developed different ways of blocking infection both in vitro and in vivo that in turn resulted in significantly reduced mortality rates in animal models of severe infectious diseases. In conjunction with a company in Sweden, the group now has filed five patents covering this part of the investigation.

“Most of our work was performed with one pathogen, but it would be of great importance to investigate whether there is a general mechanism that is employed by other bacterial species as well, since it is our aim that the same substance could be applied to any kind of bacterial infection,” said Dr Herwald. “However, what is very important is that some substances can only be given at certain stages of the infection process. For instance, if a host effective system is already systemically activated, the application of a specific inhibitor will be only marginal or without any effect, since the damage had too far progressed.

“Severe infectious disease can progress extremely rapidly. For example, a patient comes to the hospital in the morning not feeling very well and, if there is a severe infection, this patient may die after lunch. So early diagnosis is very important and the mortality rate statistics show that for each hour a proper treatment is delayed the mortality rate is increased by 7.5 per cent. That is a very high rate, and in order to address this we would like to identify proteins that could serve as markers for early diagnosis.”

But while the laboratory tests continue and the group has established that a lower mortality rate can be achieved with substances that block the contact system, the situation is — for the moment — only one in theory as it applies to ill human beings. “A clinical problem like sepsis can be caused by a variety of bacteria. However, we work with an animal model using inbred mice challenged with the same bacterial strain. All animals become infected and get treatment at the same time,” said Dr Herwald. “Unfortunately, this doesn’t resemble the clinical situation at all — it is much more complicated.

“The models we have at the moment are, therefore, very limited and it is impossible to establish more advanced models that would possess all features of a real disease. For example, we work with a human pathogen that doesn’t cause the same disease in mice, so we cannot expect that what is observed in the animals also happens in humans. In a clinical trial, the problem is that physicians can administer a substance that is expected to cure the patient.

“However, it had happened that the situation became even worse and when it comes to such point this study has to stop for ethical reasons. So many companies are not interested in running clinical trials because the high failure risk coming at a very late stage. These are the real challenges that we have to face.

“Because of recent research in this area the thinking has shifted from antibiotics to actual targets attacking the human host and now we have better understanding of how mechanisms are regulated. Notably, activated protein C (APC), a coagulation inhibitor, is only drug that was recently introduced into hospital to treat patients suffering from severe infectious diseases. These are promising developments, however APC has some severe side-effects and can be given to a limited group of patients. It is therefore important to continue the research of HSE and identify novel targets for drug development. In the future, clinicians and researchers have to look much more carefully at what stage the patient is in — for instance whether he/she is in an inflammatory or anti-inflammatory phase — and I think we will have better tools to diagnose this and develop the therapy accordingly.

“I have been running this project for 10 years and it could go on for another 30 years. There is always something to do. One breakthrough in my lab was last year’s finding that the mortality rate could be reduced by blocking the contact system. That was a very major discovery but, of course, we would like to confirm these findings with other pathogens and I think that is something that could happen over the next few years.”