Research Briefings

Sebastian G.B. Amyes
Carbapenem resistance in Acinetobacter baumannii; an important stage leading towards pan-resistance

ACINETOBACTER BAUMANNII IS AN IMPORTANT HOSPITAL PATHOGEN THAT IS OFTEN RESISTANT TO ALL ANTIBIOTICS. WE FOUND ALL STRAINS OF THE SPECIES CARRY "HIDDEN" □-LACTAMASES THAT HAVE THE POTENTIAL TO CAUSE RESISTANCE TO THE FINAL DRUG OF CHOICE, CARBAPENEMS. THERE ARE NO NEW ANTIBIOTICS ABLE TO TREAT ACINETOBACTER BAUMANNII INFECTIONS SO OUR WORK IS EXAMINING HOW TO PRESERVE THOSE THAT WE HAVE

S.G.B. Amyes
Professor

University of Edinburgh
Tel: 0131 242 6652

Email:
Sebastian.Amyes@ed.ac.uk

Antibiotics were the major medical discovery of the 20th century, their introduction alone increased average life expectancy by 10 years whereas curing all cancers would increase life expectancy by two years. However, their efficacy has been compromised by the emergence of bacteria resistance; so much so that some infections are no longer treatable. This is most prevalent in hospital-acquired infections which are now responsible for 4% of all deaths. Our research is examining why some bacteria have emerged as primary hospital pathogens. The well-known pathogens such as MRSA, are Gram-positive and are relatively easy to treat as new drugs are being brought on stream. However it is now well-recognised that that the major problem now facing us are infections caused by Gram-negative bacteria. Our research has examined the progression of Gram-negative bacteria to multidrug resistance. Most recently, we have described the species Acinetobacter bauamnnii, this was a species of bacteria that was unheard of in clinical medicine until the 1970s however, it has continuously been selected by the overwhelming exposure to antibiotics faced by bacteria causing hospital infections.

We were the first to show the reason why some strains of the bacteria became resistant to the final antibiotics available to treat it, the carbapenems. We found that the most resistant strains encoded a novel, previously undetected beta-lactamase, which we call OXA-23. As this enzyme, nor anything like had been found before, to find it we took amino acid sequences of the active site regions of common □-lactamases, as these are the most comserved, and created degenerate primers from them. These primers would provide all the nucleotide combinations for this amino acid sequences. We were then able, by PCR, to amplify the section of DNA covering the active site. From this information, we were able to start selective amplification by PCR on the margins of this region and buildup the sequence of the whole gene and its control points. This discovery led to a plethora of closely related enzymes described by other workders. Since this discovery, this has now been found in bacteria from 60 hospitals in the England.

Furthermore by similar techniques, we went on to find that every Acinetobacter baumannii strain possessed another enzyme, sharing 60% similarity with OXA-23, that did not confer carbapenem resistance. This enzyme, which we called OXA-51, was the first of over 50 almost identical enzymes, grouped as OXA-51-like, that we have found in this species. These enzymes shown in the figure below can be identified as having followed identifiable substitutions in their evolution; however, they tend to cluster around

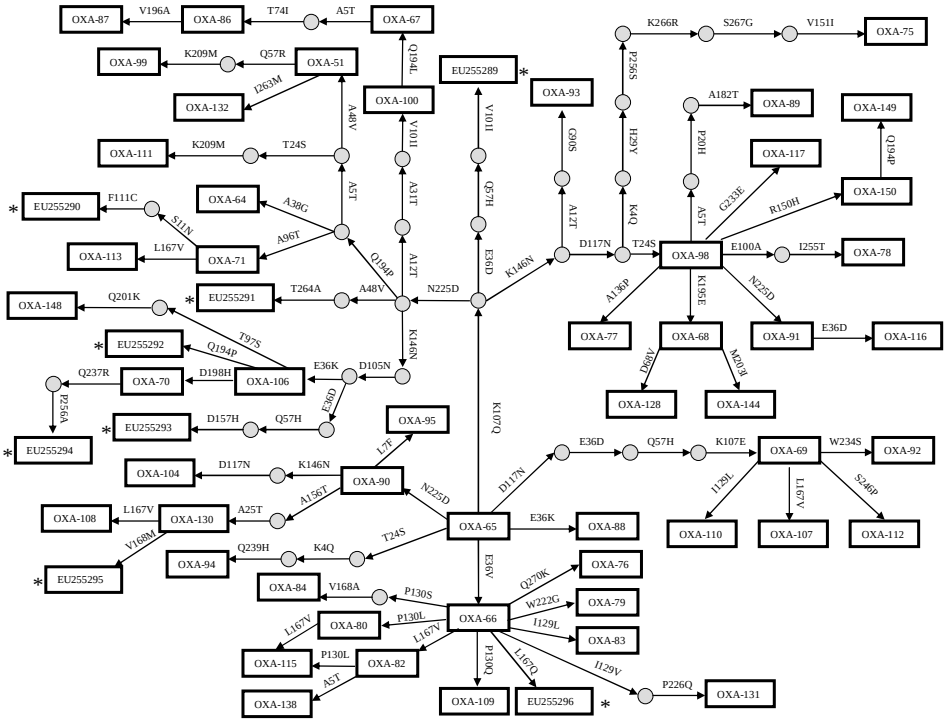

Fig 1: OXA-51-like enzyme map showing all the "hidden" chromosomal □-lactamases in Acinetobacter baumannii. Amino acid substitutions are listed with respect to OXA-65. B.A. Evans PhD, Edinburgh 2009

three enzymes, we discovered, OXA-66, OXA-69 and OXA-71. Each of these enzymes has now been found to be the "resident" OXA-51-like enzyme in the three major clones of Acinetobacter baumannii found around the world. So close is this associated that it can be used to type the bacteria.

We are now sequencing our new strains by full genome sequencing, this gives us a convenient method to examine the control mechanisms that adjust the level of these enzymes. It seems that each of these OXA-51-like enzymes has the potential to confer carbapenem resistance by altering it control. If this is proved to be the case, then the battle against these bacteria will become significantly harder.

Much of this work has been performed by PhD students and we have supervised 40 students to their PhDs.

SELECTED REFERENCES

S. Brown, H.-K. Young, and S. G. B. Amyes. 2005. Characterisation of OXA-51, a novel class D carbapenemase found in genetically unrelated clinical strains of Acinetobacter baumannii from Argentina. Clin.Microbiol.Infect. 11:15-23.

S. Brown and S. G. B. Amyes. 2006. OXA □-lactamases in Acinetobacter; the story so far. J.Antimicrob.Chemother. 57:1-3.

B.A. Evans, A. Hamouda, and S. G. B. Amyes. 2007. OXA-type □-lactamases in Acinetobacter baumannii: emerging from the shadow of the extended-spectrum b-lactamases. Rev.Med.Microbiol. 18:63-72.

T. Schneiders, J. L. Findlay, and S. G. B. Amyes. 2008. Efflux pumps in Acinetobacter baumannii, p. 105-127. In: E. Bergogne-Berezin, H. Friedman, and M. Bendinelli (eds.), Acinetobacter Biology and Pathogenesis. Springer, New York.

S. G. B. Amyes 2010. Antibacterial Chemotherapy. Oxford University Press. Oxford.

Research supported by Medical Research Council, Wellcome Trust, DEFRA, Scottish Parliament