Antibiotic resistance: what have we learned and where do we go from here?

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Antibiotic resistance has been accepted as a potential threat to the future of antibiotic therapy ever since the discovery of the first penicillin-resistant strain of *Stapyhlococcus aureus* in 1947. Now, almost 60 years later, we are facing a possible global pandemic as bacteria continue to evolve into multiple drug-resistant species and the healthcare industry struggles (and fails) to keep up. As it becomes increasingly apparent that industry is no match for nature, so too has it become more obvious, that in order to prevent a return to the pre-antibiotic era, we must adapt our focus and research in order to better understand the mechanisms bacteria use to outwit and evade antibiotic agents. Dr Joseph Blondeau of the University of Saskatchewan (SA, Canada) has been working in the field of antibiotic resistance as a Clinical Microbiologist for almost 15 years and in this issue of *Therapy*, shares his thoughts on the threat of antibiotic resistance, lessons from the past and his vision for the future of research and antibiotic drug discovery.

How did you first become involved in the issue of antibiotic resistance?

We started investigating antimicrobial agents and antibiotic resistance back in 1992/93 when I was fresh out of training and had my first hospital position. We became interested in certain trends that we were observing in our own hospital for which we didn't think there was a lot of literature, and as a result, we started to do our own small investigations locally, these extended to a national study and we ended up publishing our first papers after that.

Whilst resistance to antibiotics is widely recognized, do you think enough is being done to highlight the severity of the threat?

I don't think I do. I think that resistance is well recognized. I do believe that we see this as being a global pandemic with very few exceptions – I mean, there are no bugs for which there isn't resistance to at least one antibiotic – I think that is well recognized. How do we do more? I think there is a lot of surveillance work going on that probably forms the bulk of the literature, but the surveillance data doesn't necessarily get to the root of the problem, it just tells us that the problem exists, so to my way of thinking, we do need to spend more time trying to study, in much greater detail, the factors that lead to the selection of resistance and subsequent dissemination. We must determine if there are any interventional strategies that can be performed, at the prescribing level, in order to prevent resistance from occurring. Once you have the problem then you have a problem. In an ideal world, the best way of dealing with resistance is to prevent it from occurring, so in some regards, I say yes, we're doing a lot to characterize resistance and to survey for it, but I do think that there is room for improvement in trying to stop it before it starts. Unfortunately, resistance is insidious and may not be totally preventable.

The inevitability of antibiotic resistance places a dark cloud over investment in the development of new antibacterial agents – do you think it's time we 'gave up the ghost' and concentrated our efforts into understanding, with a view to reversing, already existing resistant mechanisms, or is there still a future for drug development?

I think both. The advances in antimicrobial therapy that have been made over the last 20–30 years have actually been quite encouraging. But you just can't develop a new drug in anticipation that it's going to fix all of your resistance problems without trying to get at the source of why these resistance issues are occurring, so I think there are two fronts that we have to move on. First, we have to redefine how it is that we're using existing drugs in order to maximize therapeutic benefit; maximizing therapeutic benefit, in my mind, means having a favorable clinical outcome while, at the same time, maximizing the microbiological and

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pharmacological advantages of these drugs to minimize the likelihood of selection for resistance. I think this is essential and we have to do that with older agents for sure. Second, with newer agents, I think we have to look toward regulatory bodies to say, ok, approving a drug based on clinical outcome alone is insufficient. Again, I think we should be looking at new drug approval based on not only the clinical outcome and safety-related issues, but whether or not there's an increased or decreased likelihood that it *may* have some propensity to select or not select for resistance. We now have measurements that are capable of examining this question for some compounds.

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What role do you think the pharmaceutical industry should play in resolving this issue? Or do you think it's the responsibility of industry in conjunction with regulatory bodies to address this?

Once again, I think its both. I think the pharmaceutical industry has a huge role to play here, and I think in many instances, the pharmaceutical industry has been more proactive than perhaps either expert review groups or regulatory bodies recognize. We live in a world where we tend to manage our problems after our problems have occurred. We tend to do a lot of crisis management and I think with the issues of resistance, the best way of dealing with this is to be proactive and try to minimize resistance from occurring. I think industry has an important role to play in trying to find products that may fit this criteria (i.e., active against resistance strains), but also at the same time promoting appropriate use of their drugs.

So do you feel that the pharmaceutical industry is currently not doing enough in terms of promoting responsible drug use?

No, I do think that some companies are doing more than others, and I don't want to paint all with the same brush. I do feel that there are some initiatives in industry that are really quite encouraging, and that some of those initiatives need to be more spread out. Even simple initiatives, such as hand washing promotional posters, are extremely useful. Many current microbiological and pharmacological advancements have been funded by grants from industry.

Do governing bodies then have a role to play in bringing together regulatory agencies and the pharmaceutical industry to discuss and decide upon possible guidelines?

Well, possibly. I think that we [the government] – being a government employee – tend to react when we have a problem, we tend not to react when we don't have a problem. So, I think that there's a proactive role that's required, both from the regulatory agencies and from government, in conjunction with industry. Typically, governments don't invest in drug development. That tends to be in the private sector. But, at the same time, I think you cannot be too strict in terms of regulatory requirements or else you're not going to have any drugs – so there's a healthy balance, but I'm not sure if I know where that balance is.

On January 1, 2006, the EU banned the feeding of all antibiotics and related drugs to livestock for growth-promotion purposes. In the USA, a growing number of organizations are attempting to get the Preservation of Antibiotics for Medical Treatment Act passed. Since it has been estimated that 70% of antibiotics (and related drugs) in the USA are actually used in animals (Union of Concerned Scientists), what effect do you think the passing of this bill, and subsequent incorporation into farming practices, would have on the current and future threat of antibiotic resistance?

Well, a couple of things. First, we know that drug use precedes resistance – I think that most people would agree on that point. We know that an enormous quantity of antibiotics were used for promotion in livestock. There are a number of concerns about the use of antibiotics for growth promotion. Some data show a link between the level of antimicrobial consumption and the risk of antibiotic resistance, and in other instances, the data are not entirely clear. However, i do feel that, from a practical point of view, it does make sense that if we could eliminate some drug use it may have some positive role in impacting on resistance; however, I will also state that I see drug use for growth promotions as being very very different from the use of drugs in veterinary medicine for the treatment of infectious diseases. Those are two separate items, and I don't have as much of an issue with drug use for the treatment of infection as I do with drug use purely for growth promotion.

What are your thoughts on the use of complimentary and alternative medicines, such as homeopathy, vitamins and mineral supplementation and hydrotherapy, in place of antibiotics, or do you see that maybe there is room to use them together?

Well, possibly. It's not an area that I have an awful lot of experience with. I'm a clinical microbiologist and I kind of swing in my own little world, but I would say that we do know that there are a number of infectious diseases and presentations where, if an antibiotic was *not* used, the patient would spontaneously resolve the infection. Certainly, in patients with mild-to-moderate disease, that's probably true. Having said that, there is absolutely no way, based on the information that I know at this point in time, that you can look at patients and predict which one would have a successful outcome and which one would have a complicated course and maybe even deteriorate and, heaven forbid, die. So, as a consequence, it has always been my position that in a patient that has a high likelihood of having a bacterial infection, antibacterials should be used and used appropriately. I don't necessarily see other types of intervention as being a replacement for that – they may be used in concert with it, but I don't see it as being a replacement.

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What do you feel are the most important lessons we have learned over the past 50 years and how can we use this knowledge to move forward?

Well, the first important lesson that we've learned is that we didn't pay attention to the lessons that we've learned. When penicillin was first released, within 10 years, 80% of *S. aureus* strains produced penicillinase and were resistance to penicillin. I think it was Fleming that wrote in 1945 'But I would like to sound a note of warning...It is not difficult to make microbes resistance to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them and the same thing has occasionally happened in the body'. This was followed by Harington in 1957, who wrote 'In spite of the great advances that have been made in recent years in the chemotherapeutic treatment of infectious diseases – advances that have brought under some measure of control the majority of protozoal and bacterial infections and some helminthic infections – the subject of chemotherapy remains distressingly empirical' [1]. So, we learned this lesson about the potential for antimicrobial resistance an awful long time ago, and we ignored it. One reason why we ignored it is because we looked towards the pharmaceutical industry to always make the next best drug to deal with our resistance problems, and we're getting to an end, at least based on my knowledge, of novel targets that may be present within bacteria and that can be exploited. So, what have we learned? We've learned that microorganisms are incredibly adaptive and can develop resistance to even the most powerful drugs. The other thing that we have learned is that clinical outcome is not the only measurement for the success of an antibiotic. You have to take into account the pharmacokinetic and pharmacodynamic parameters and potency, as well as microbiological potency and microbiological outcome and breakpoints, as a component of the successful treatment of a patient. In an ideal world, a patient would get better from infection, while at the same time you've prevented selection for resistance during that process. Learning this lesson would be helpful, but mostly we've learned that we didn't pay attention to what we should have been learning.

Bibliogprahy

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