



# PathWay

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA



APRIL 2013 | Published by RCPA

Issue #024

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- Superbugs have lost some battles, but they may still win the war
- Familial hypercholesterolaemia might be too much of a mouthful
- Sudden cardiac deaths can also save lives
- Oral and maxillofacial pathologists fill a vital role in medicine

## Introduction

There has been a lot of coverage about antimicrobial resistance lately with headlines warning of catastrophic consequences if we don't act with urgency. These headlines are right. Professor John Turnidge, clinical microbiologist at South Australia Pathology, explains why.

We have followed up another topic from February's Pathology Update conference with an article on why we should keep familial hypercholesterolaemia in mind, despite its unfortunate name!

Finally, we've looked at how and why forensic pathologists solve unexplained cardiac deaths, and highlighted the specialist work of oral and maxillofacial pathologists.

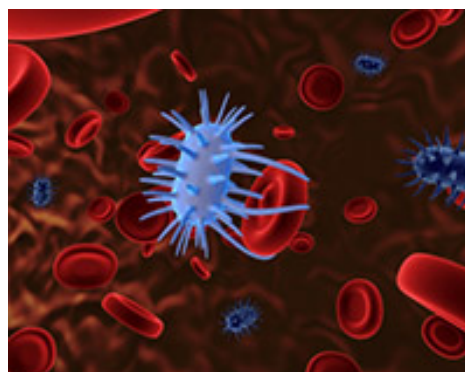
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## Interesting Facts

# More than 40%

The number of children with acute diarrhoea in developing countries who don't receive the necessary oral rehydration therapy

## Superbugs have lost some battles, but they may still win the war



The name 'superbug' conjures up images of an old-fashioned 'goodies against the baddies' movie plot. On the good side sit the antibiotics whose job it is to protect humanity against wayward bugs,

# More than 40%

The number of children with acute diarrhoea in developing countries who receive unnecessary antibiotics

# About 440 000

The number of new cases of multidrug-resistant tuberculosis (MDR-TB) which become known annually, causing at least 150 000 deaths. Extensively drug-resistant tuberculosis (XDR-TB) had been reported in 64 countries as of March 2012

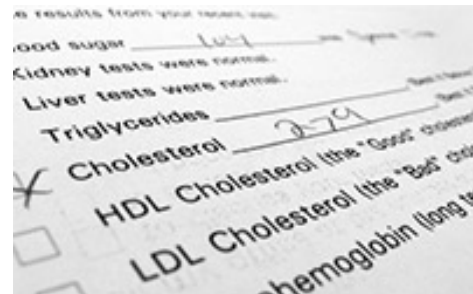
Source: World Health Organization

and on the bad side are the superbugs that just keep spoiling the party by causing havoc and, in some cases, death. But unlike the movies, there is no scripted happy ending. Only a scenario where we must start using antibiotics more cautiously and selectively so they don't become yesterday's heroes.

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## Familial hypercholesterolaemia might be too much of a mouthful

If there's one thing familial hypercholesterolaemia suffers from, it's an image problem. Evidence is now leaning towards a prevalence of about 1 in 200, yet fewer than five percent of the expected cases have been identified in Australia. Associate Professor David Sullivan, chemical pathologist and physician at Royal Prince Alfred Hospital in Sydney, says that if it had a simpler name, like diabetes, then it might be easier to get the message out there about how common yet serious this condition really is.



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## Sudden cardiac deaths can also save lives

The heart is an amazing organ. It is both electrical and mechanical in nature and beats approximately 100,000 times a day sending about 75,000 litres of blood through the average adult body. It also keeps the blood flowing through about 97,000 kilometres of blood vessels to feed the organs and tissues. But when something goes wrong and it stops, causing sudden cardiac death, there may not be any obvious clues about what went wrong. That's when forensic pathologists step into the picture.



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# Oral and maxillofacial pathologists fill a vital role in medicine

As far as specialties go, oral and maxillofacial pathologists reside at the very tip of the pyramid. With just 10 to 12 of these specialists dotted around Australia and New Zealand, it's probably also a fair bet that not many people even know about them – until they need them.



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## Superbugs have lost some battles, but they may still win the war



The name 'superbug' conjures up images of an old-fashioned 'goodies against the baddies' movie plot. On the good side sit the antibiotics whose job it is to protect humanity against wayward bugs, and on the bad side are the superbugs that just keep spoiling the party by causing havoc and, in some cases, death. But unlike the movies, there is no scripted happy ending. Only a scenario where we must start using antibiotics more cautiously and selectively so they don't become yesterday's heroes.

"There has been a problem with antimicrobial resistance since day one dating back to the 1940s," explains Professor John Turnidge, clinical microbiologist at South Australia Pathology. "Basically, resistance to antibiotics has been accumulating and now some organisms are resistant to everything."

Antimicrobial resistance (AMR) <sup>[1]</sup> is the resistance of a microorganism to an antimicrobial medicine to which it was previously sensitive. It is a consequence of the use, and often the misuse, of antimicrobial medicines such as antibiotics, and develops when the microorganism mutates or acquires a resistance gene.

While Prof Turnidge says the number of superbugs is hard to quantify, there are four major human pathogens that are now resistant to multiple antimicrobials. These are *E. coli* (a common cause of urinary infections) as well as *Staphylococcus aureus* ('golden staph'), *Acinetobacter* and *Pseudomonas aeruginosa* (all common causes of a variety of diseases

ranging from pneumonia to serious blood or wound infections).

When faced with headlines warning about 'catastrophic threats from superbugs', Prof Turnidge asks if you can you have a catastrophe that lasts 20 years?

"We have reached the top of the problem and it is the beginning of the end of being able to treat organisms with antibiotics unless we do something," he warns. "We need to learn the lessons of the past and find ways to fix the problem."

The professor's 'to do' list includes finding new antibiotics, educating society about the harm of prolifically using antibiotics and reset their expectations, and pooling government and non-government resources to change the prescribing habits, and rates, of antibiotics.

It all sounds simple, but each point masks a myriad of complexities. For example, the economic incentives for companies to invest in new antibiotics are quite restrictive, while weaning everyone off the 'magic bullet' of using antibiotics unnecessarily is also complex.

"The shining example of how dire the problem is now is the gram-negative bacteria which carry the New Delhi metallo-beta-lactamase enzyme, called NDM 1, which is harboured by up to 200 million people in India," he says. "India has a high and intense usage of antibiotics and poor hygiene in many places so superbugs, such as NDM 1, are thriving. So far about 10 to 12 cases of NDM have popped up in Australia and New Zealand."

The level of antibiotic-resistant infections strongly correlates with the level of antibiotic consumption. Pathologists work on the front line in terms of detecting the resistance in the first place and contributing to the national database about AMR. However, another issue is that there is currently no way to know how bad the problem is in the community. One example is methicillin-resistant *Staphylococcus aureus* (MRSA) which is a bacterium responsible for several difficult-to-treat and serious infections in humans.

"Most hospitals keep records of their MRSA infections, but it's a catch 22 situation. It is a growing problem in the community yet we don't know how bad it really is. Western Australia is the only state and territory where every case is notifiable."

*Staphylococcus aureus* bacteraemia (SAB) kills thousands of people every year, and could be considered the 'canary in the coalmine'. Predictions such as people dying from ordinary infections because they can no longer be treated with antibiotics could be a reality in the not too distant future. And if this happens it may be a case of the superbugs losing a few battles along the way, but eventually winning the war.

[\*] Antimicrobial resistance is also covered in [ePathWay issue #008](#)

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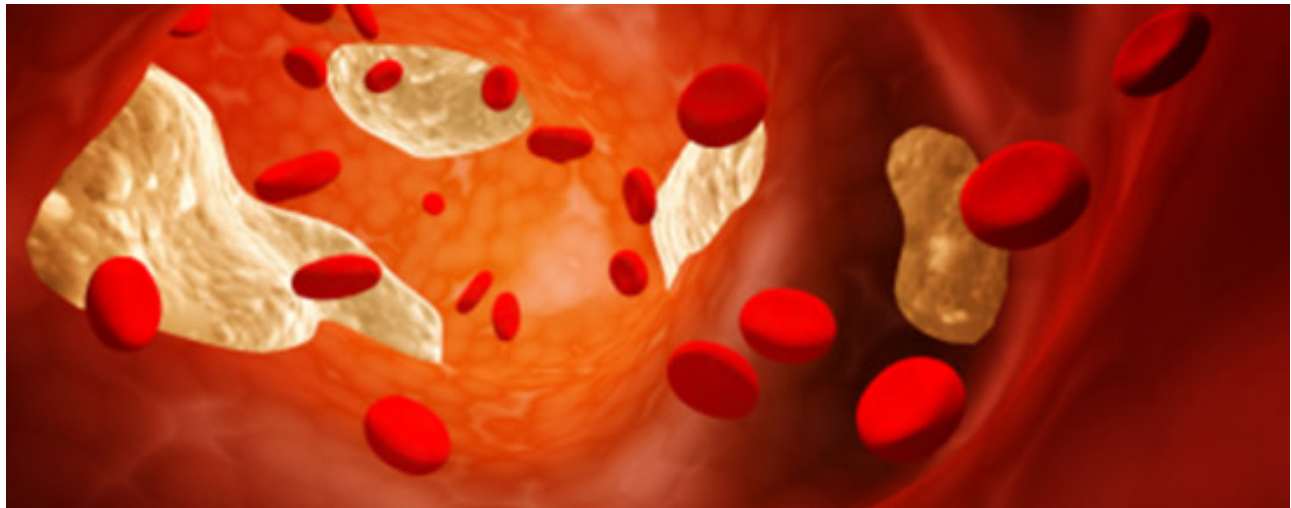




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## Familial hypercholesterolaemia might be too much of a mouthful



If there's one thing familial hypercholesterolaemia suffers from, it's an image problem. Evidence is now leaning towards a prevalence of about 1 in 200, yet fewer than five percent of the expected cases have been identified in Australia. Associate Professor David Sullivan, chemical pathologist and physician at Royal Prince Alfred Hospital in Sydney, says that if it had a simpler name, like diabetes, then it might be easier to get the message out there about how common yet serious this condition really is.

"Familial hypercholesterolaemia is a big name for a simple condition that is completely treatable," he says. "It's familial, so it has genetic causes and is probably the most common potentially fatal of all of the genetic conditions."

Familial hypercholesterolaemia is a disorder of excessive low density lipoprotein (LDL or bad) cholesterol<sup>[\*]</sup>. The body can't remove this type of cholesterol from the blood due to a genetic defect, resulting in high levels of bad cholesterol. This, in turn, increases the likelihood of developing narrowing of the arteries (atherosclerosis) at an early age.

But that's not all. This disorder begins at birth, is passed down through families and can cause heart attacks at an early age. And you only need to get the abnormal gene from one parent in order to inherit the disease. A/Prof Sullivan says that if a

person is affected, the risk to everyone who is a first degree relative is 50%. So, there should be a strong incentive to find people with it.

"This disorder is one of the main risk factors for cardiovascular disease but there isn't a proper policy in terms of detecting or even screening for it. We only find cases by chance at present," he says.

A/Prof Sullivan says hints that people might have familial hypercholesterolaemia include:

- a high LDL cholesterol level
- a family history of high LDL cholesterol levels
- a family history of heart attack and stroke at an early age
- a rim of white around the iris of the eye (called an arcus)
- lumps of cholesterol in the tendons (especially the achilles and on the back of the hand) which can be felt through the skin.

High LDL cholesterol levels can be easily detected by a simple blood test. A/Prof Sullivan says there is also a suggestion on the table in Australia at present that reminders be automatically included on pathology reports for GPs to consider checking for familial hypercholesterolaemia when they come across a person with a high LDL cholesterol level.

Of course, the test that really nails it is a genetic test. A/Prof Sullivan says that finding the index case (the first one in a family) and then using cascade screening to find all of the family members with familial hypercholesterolaemia is the best approach. He says in this case, the genetic diagnosis is as much a management tool as it is a diagnostic test, but there is a process that should be followed.

"Like any genetic test that has familial implications, it is best handled by a specialist genetic service where counseling is offered before and after the tests," he says. "These services are also more committed to cascade screening."

But for now it's a challenge just getting the message out there about familial hypercholesterolaemia. And if its unwieldy name is adding to its image problems, then perhaps we should abbreviate it to 'FH' for a while. That might get the gist of the name out there, and if it increases the profile of this common yet treatable genetic condition, then we might be finally cooking with the good oil.

 Cholesterol is covered in [ePathWay issue #006](#)

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"If a person dies from sudden cardiac death there will always be a post mortem if a doctor cannot be certain of the exact cause of death to put on the death certificate," explains Dr Beng Ong, forensic pathologist at Forensic and Scientific Services in Queensland Health.

"We try to find the cause of death by examining the heart. We look for clues to see if the death was for example due to a heart attack, disease of the heart muscle called cardiomyopathy, inflammation of the heart muscle called myocarditis or perhaps a disorder of the cardiac rhythm."

If the autopsy is negative (no cause of death was discovered), Dr Ong says forensic pathologists once again review the patient's medical history to see if there is a clue pointing to other causes of death. Examples might be a neurological problem

such as fits, a drug overdose or even natural causes. But this doesn't happen very often. Dr Ong says his laboratory examines hundreds of sudden cardiac deaths a year, and only about one to three result in negative autopsies.

"In these cases we review the post mortem to make sure we didn't miss anything, and perhaps do more investigations to make sure we have covered everything. When all of those results come back, and if they are negative, we will again look for a disorder of the cardiac rhythm. This is because the post-mortem results for these conditions are typically negative."

Dr Ong says molecular tests may be used to look for genes associated with heart disease including abnormal cardiac rhythms, but these tests are expensive because Medicare does not cover them when they are a part of an autopsy. For this reason they are not routinely performed, but the pathologist may write to the person's family advising them to consult their doctor with a view to having these tests themselves if they feel there is a strong case for them to do so.

"There are genes known to be associated with cardiac diseases and molecular tests can be performed to see if these genes are present," he says. "If we find the cause and it's a genetically-based disease, or we suspect this is the case, then we can advise the family and they can seek further tests and potential treatment."

Finding the cause of a sudden cardiac death can be very difficult, but it's also important. This is because many cardiac conditions are familial and, for each diagnosis, about 10 high-risk relatives can be identified as potentially having that disease. Molecular techniques can help this process, and since about 10 relatives can benefit from the information, forensic pathologists also practise preventative medicine – in a roundabout way.

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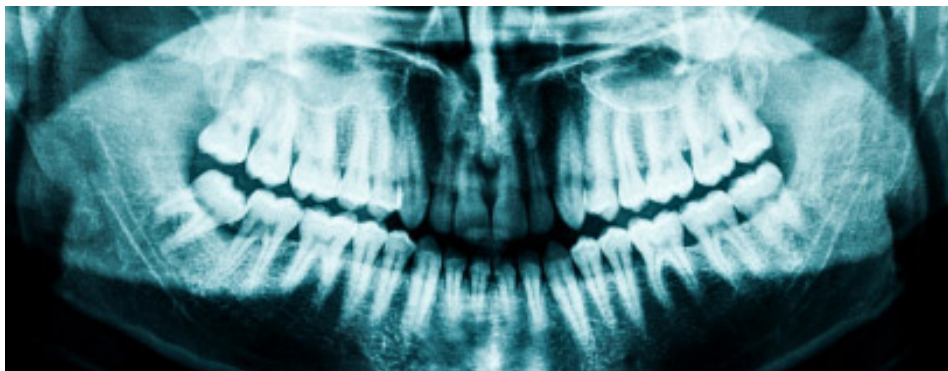
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As far as specialties go, oral and maxillofacial pathologists reside at the very tip of the pyramid. With just 10 to 12 of these specialists dotted around Australia and New Zealand, it's probably also a fair bet that not many people even know about them – until they need them.

"Oral and maxillofacial pathology incorporates diseases of the teeth, oral mucosa, jaws and the orofacial region," explains Dr Anna Talacko, oral and maxillofacial pathologist at Dorevitch Pathology in Melbourne. "We provide reports to our colleagues, who include oral and maxillofacial surgeons, specialists in oral medicine and other dental specialists. We also report for general dentists, general medical practitioners and medical specialists such as ear, nose and throat specialists who might, for example, take a biopsy of the tongue and send it to us."

Dr Michael Aldred, oral and maxillofacial pathologist at Dorevitch Pathology in Melbourne and Honorary Secretary and recent Chair of the RCPA Faculty of Oral and Maxillofacial Pathology, says most oral and maxillofacial pathologists have dental training. This means they have an extra layer of understanding of diseases of the mouth, and of the specialist terminology when compiling reports for their dental colleagues.

"The terminology can be confusing, and we issue reports dentists and dental specialists can understand," he explains. "We may also speak with clinicians by phone and review clinical and radiological (X-ray) findings which means the patient receives better care and potentially avoids unnecessary treatment."

Training to become an oral and maxillofacial pathologist involves dental or medical training followed by five years of postgraduate training in two laboratories approved by the RCPA. It is both a medical and dental specialty and has traditionally



been combined with training in oral medicine via a dental postgraduate degree. Graduates may work exclusively in the area of oral pathology, but some undertake additional work such as clinical oral medicine, research or an academic position.

So, what sort of cases do oral and maxillofacial pathologists examine and diagnose? Dr Aldred says they handle diseases of the salivary glands including tumours, diagnose a range of cysts of the jaws and surrounding soft tissues and report on bone lesions and odontogenic tumours (tumours which arise from tooth-forming tissues).

“Odontogenic tumours can be difficult to diagnose because they often don’t look like teeth. They are also uncommon, are particular to the jaw and can mimic the appearance of tumours arising elsewhere such as from the brain, although this is rare,” explains Dr Talacko.

“Another example is that we might diagnose a skin rash in the mouth, which looks different in the oral environment because the saliva changes the appearance compared to what it might look like on dry skin.”

Dr Talacko says salivary gland pathology is also notoriously difficult, and an oral and maxillofacial pathologist may consult colleagues at a local, national and international level to ensure the correct diagnosis. However, for pathology involving teeth she doesn’t have to go further than her colleague, Dr Aldred, who has a particular interest in inherited diseases of the teeth and is considered a world expert in this area.

If you didn’t know that teeth could have inherited diseases, then again you’re probably not alone. But understanding these diseases is important because they may not only affect the rate of development of baby and adult teeth, but they can also reflect a wider syndrome or disease affecting the normal growth and health of other parts of the body. These inherited diseases represent just one area where oral and maxillofacial pathologists fill a vital role in medicine.

The fact that most of these specialists are dentally trained also means that they can communicate with a wide variety of health practitioners to obtain the best outcome for the patient. And like any specialty area, you may not know what they do until you need them and have a chance to appreciate their specialist skills and expertise. In fact, the diagnosis of any disease of the mouth or jaw may require the unique specialist expertise of an oral and maxillofacial pathologist.

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