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In this Issue

Rob Siebers, Editor

Each year the NZIMLS invites a prominent New Zealand medical laboratory scientist or pathologist to deliver the TH Pullar Memorial Address at the Annual Scientific Meeting, This year's recipient was Ken Beachey, formerly from Canterbury Health Laboratories and previous President, who's address, entitled "Show your true colours: values in the workplace" is in this issue.

Dennis Mok and colleagues present an applied tool based on conformance requirements identified in ISO 15189:2012 which can be used to audit the conformity status of the use of API 20 E in the areas of acceptance testing as well as calibration and metrological traceability.

Juliet Elvy, on behalf of the New Zealand Antimicrobial Susceptibility Testing Committee, presents this Committee's guideline "Minimum laboratory requirements for the detection of carbapenemase-producing Enterobacteriaceae from clinical samples and screening specimens". New Zealand medical microbiology laboratories are expected to comply with the recommendations outlined in this guideline.

Sharda Lallu and colleagues report on a case of primary pulmonary papillary adenocarcinoma mimicking papillary thyroid carcinoma. With the use of appropriate immunohistochemistry the proper diagnosis was made.

The Pacific Paramedical Training Centre (PPTC) in Wellington was formed in 1980 to provide appropriate training and support for medical laboratory staff in the Pacific Islands. Ron Mackenzie, co-founder of the PPTC, has published a book detailing the first 30 years of its operation. A review of this fascinating history is in this issue.

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2018 NZIMLS CALENDAR
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Date	Council	Contact
23-24 November	Council Meeting	fran@nzimls.org.nz
Date	**Seminars**	**Contact**
10 November	Mortuary SIG, Wellington Hospital	Samantha.marshall@wellingtonscl.co.nz
17 November	Immunology SIG, Wellington Hospital	sarah.burge@wellingtonscl.co.nz
23 March 2019	South Island Seminar, Commodore Hotel, Christchurch	
Date	**Conference**	**Contact**
17-19 September 2019	South Pacific Congress, Brisbane Convention Centre, Australia	fran@nzimls.org.nz

TH PULLAR ADDRESS

Show your true colours: values in the workplace

Ken Beechey

Mr President, council members, distinguished guests and speakers, fellow scientists and technicians, it is a great privilege to be invited here today to present the TH Pullar address. A very daunting task, particularly for a recently retired scientist who thought his presentation days were over and discarded all his course notes and records. Today my talk will be on the importance of personal and leadership values in the workplace by reflecting on my 45 year career in medical laboratory science. Anyone who knows me well will understand that management theory does not always sit comfortably, so my intent is to deliver the sentiment of the content mainly from the heart rather than the text book.

TH Pullar

Firstly, it is traditional and right that we open with acknowledging the role that TH Pullar played in the development of medical laboratory science in New Zealand. Dr Thomas H Pullar (or Thos as he was known) was born in New Zealand in 1907, was mainly educated in England and Scotland before returning to Palmerston North Hospital in 1936 where he worked as a pathologist for 25 years. He was always a great advocate for the development of our profession and was heavily involved with the formation of the Medical Laboratory Science Board. His work for the advancement of medical laboratory science included his involvement with the drafting of conditions of employment and preparing the syllabi for the intermediate examinations.

Thos Pullar passed away in August 1966. A lifelong teacher and champion for the profession, we again take this time to recognise his significant contributions to medical laboratory science through the T H Pullar address.

Icons, geniuses and mavericks

The theme for the conference this year is Icons, Geniuses and Mavericks. For many New Zealanders examples of these could be the likes of Ernest Rutherford, Edmund Hillary, Kate Sheppard or perhaps Richie McCaw and Winston Peters. In keeping with this magnificent aviation venue, we should include Richard Pearse a farmer from Timaru and aviation pioneer who in 1903 possibly performed the first manned flight, also Jean Batten for her record breaking solo flights. You will all have your own ideas on who fits into these categories.

As a child I discovered the beautiful game of football, 1966 being the only World Cup success for England. The football icons of the time were the likes of Bobby Moore, Jimmy Greaves and George Best. Now George Best was clearly an icon of the sport and his ability on the ball pure genius. He was also described as a bit of a maverick. As if to prove this point, when asked how he lost his fortune he is famously quoted as replying: "*I spent a lot of money on booze, birds and fast cars. The rest I squandered.*" Sadly, his career was short lived and he succumbed to the effects and complications of alcoholism. I would suggest to you that whether someone is an Icon, Genius, Maverick or all three is in the eye of the beholder.

Iconic leaders

The same would appear to be true with iconic leaders, that is, we all have ideas on our own icons and tend to admire those leaders whose attributes and values sit well with our own. For me it is Shackleton who's incredible trans Antarctic Expedition attempt of 1914 -17 ended in failure in terms of the proposed crossing after his ship the Endurance became trapped in the pack ice. However, the amazing story of survival of the whole expedition team under extraordinary circumstances beggars belief. His many leadership skills and his primary concern for the welfare of his men are values that I can associate with. Another of Shackleton's strengths was that, despite several of his expeditions not attaining their initial goal, he had the ability to reset his aims as the situation changed, something we can all learn from. In the words of Winston Churchill: "*Success consists of going from failure to failure without loss of enthusiasm.*" It is a good lesson to recognise that our original aims/goals are not always the best or possible end solution as any project develops, often with changing restraints. I recommend you read up on Shackleton's expedition if you haven't already done so.

Whether the leader you admire most is Shackleton, Martin Luther King, Ghandi, Mother Teresa or Richie McCaw, it is likely the attributes they demonstrate resonate well with your own personal values. This leads me on to the main topic for today being values in the workplace.

In my working years I worked with the maxim: **Best staff - Best Equipment – Best systems**. I believed with these in place it equated to a quality laboratory producing quality results, a laboratory where I envisaged staff would want to work and could also enjoy their work. This statement is firmly underpinned by the personal and workplace values important to me. Let's have a closer look at values in the workplace.

Core life and workplace values

Let me start with quite a bold statement attributed to Roy Disney, "*It's not hard to make decisions when you know what your values are*." It certainly makes sense to me but was not necessarily that simple in action, where we are not always empowered to make the decisions we are required to implement. What are values and have you thought what they mean to you?

Your values influence every aspect of your life from your own moral judgements to how you respond to others in any given situation. They are the essence of who you are, they set the bottom line in the decisions you make both in your personal life and the workplace arena. They guide you when to say yes or no and influence how you respond and react to others (1). I am going to initially separate core life and workplace values, however, they are naturally entwined and both affect the way you go about your daily life and work.

So first let's look at core life values: Do you know your own core life values and character strengths and what they mean to you? Typically, we will tend to identify with three to five key core values/character strengths which influence how we lead our everyday life. These are the values that make you who you are. Examples may include: Family, Love, Humour, Courage, Humanity, Learning and Justice. There are on line tools which can help identify your character strengths (2).

For me it was family, humour and a fascination with the natural world. These core life values can cause conflict at the workplace, for example: long working hours could clearly lead to tensions should family time at home be important to you. Also, overuse of any given strength can also become a weakness. Your workplace values are the deeply held principles that are most important to you about the way you work. They guide you to choose the right way to work and lead your career choices and decision making. Examples of workplace values:

- Fairness - Self-accountability
- Integrity/honesty - Teamwork
- Trust - Courage
- Quality/attention to detail - Loyalty
- Reliability/keeping promises and deadlines - Optimism
- Leading by example - Tolerance
- Showing respect - Exhibiting appreciation
- Investing in others - Humility

Honesty, fairness and teamwork values featured strongly for me. I would add here that some of these can become contradictory in certain situations. Should quality and reliability be important values, then maintaining quality and attention to detail whilst working under tight deadlines may necessitate some compromise? Are you clear about your workplace values and those of your colleagues and leaders? Are they aligned? The important point here is being: when there is meaningful and genuine alignment of your own values with those of your employer, a strong connection is created offering positive opportunities for personal growth and workplace productivity. Conversely, individuals are more likely to act with a sense of compliance and without commitment when faced with an implemented option that counters their own values system. Where these values are substantially divergent, the possibility of disruption to workplace harmony and conflict are more likely (3).

So, I now pose the following questions to you all:

- Are your values in alignment with those of your colleagues, leadership team and organisation?
- Where there is variance are you prepared to stand up and be true to your own values?

I was always aware of this but never really focussed on the importance until later in my managerial career following a leadership course. If you are working at odds with your values something has to give.

I would now like to reflect and highlight some of the important values that were an intrinsic part of a very rewarding career in medical laboratory science spanning 45 years.

A reflection on 45 years in medical laboratory science

Let's start at the beginning with your reason to care.

Reason to care

We all entered the professional with our own particular reasons to care, perhaps an altruistic desire to help and contribute in caring for people or a passion for science or for your specialised subject matter. For me, as a young teenager I spent time in an isolation ward with viral meningitis and was naturally subjected to blood and CSF testing. A staff nurse explained what happened to the samples and a little about the results which grabbed my interest in the profession at an early stage. Before being discharged I recall telling the staff nurse that I wanted to be a biochemist when I grew up.

I started my working life as an industrial chemist through a careers advisory service but this wasn't quite right for me. I had a love for science and the natural world and instinctively felt hospital laboratory work would be more suited to me. After a year I managed to obtain a junior position in haematology at the Bristol Royal Infirmary through the same careers office and the rest is history.

With the pressures of work and over time it can be easy to lose touch with your reason to care. So, I challenge you to remind yourself of your particular reason to care and ask yourself the question: is it still evident as you go through your daily work routines? Take a moment to reignite your passion/your reason to care for the essential work you perform. It really makes a difference when your passion shines through in your work.

Lead by example

In my early training years as a junior trainee scientist in Poole, I was fortunate enough to work under an enlightened chief scientist who always managed to find time for staff. He was the go to person, made himself available to all for educational purposes, discussing interesting cases and the development of new tests no matter how busy he was. He stimulated my interest and passion for haematology and I greatly admired some of the leadership characteristics he demonstrated. Throughout my career I have tried to emulate these attributes in my own working situation, hopefully I succeeded to some extent.

My next challenge for you is to find attributes and values of those leaders or colleagues you respect and where possible and you feel comfortable try to pay it forward to others. This comes with the caveat that you must be true to your own values and come across as genuine. Don't try to be something you are not, it will not sit well with you. Then: Walk the talk – be visible. As Albert Schweitzer said "*Example is not the main thing in influencing others. It is the only thing. The people around you are watching your every move and looking to emulate you*."

Respect and teamwork

Having completed my Fellowship in the UK and having gained promotion to a senior scientist position, I looked to emigrate to New Zealand for my next work venture. It was here as a young highly qualified scientist that I learned the importance of respecting your colleagues and the value of good teamwork throughout the laboratory (not just in my own department).

Respect is a two street, you need to show it to others as well as earn it yourself. Like a fish out of water coming from a new modern UK lab to a NZ community laboratory I had to quickly learn the ropes from the resident scientists and technicians. It was here, where interdepartmental relationships were closer, that I better understood the importance of the service as a whole from collection to results and that the whole service is only as good as the weakest link. This also became more evident in my later position in a multi-departmental management role.

My improved work ethic and teamwork experience gained in Dunedin was most appreciated on my return to the UK after three years. I believe I returned as a better scientist and person for the experience and learning. My messages from this experience are:

- Show respect for your colleagues regardless of qualifications or position but also continue to work at earning respect yourself. Remembering that how you are perceived is the truth to the beholder.
- Earning respect is important but showing respect is the foundation of meaningful relationships.
- Work together for improvement of whole service not just your silo area. Any laboratory is only as good as its weakest link.

On teamwork, you might like to ask yourself at the end of every week:

- What did I do to help or lend a hand at work?
- What did I do to acknowledge the work of one of my colleagues?

I'd now like to move to my next topic, professionalism. Professionalism is perhaps more of an out dated term, but nevertheless still relevant and meaningful.

Professionalism

I have always taken great pride in my chosen profession with a strong interest in professional affairs. I was actively involved with our professional bodies both in England and New Zealand which culminated with the great honour to be president of the NZIMLS. But what does professionalism mean to you? It is much more than just professional pride. The term has many different definitions available that encapsulate many behaviours including:

- Learning and maintaining expertise in all aspects of your industry
- Working to the best of your ability
- Completing high quality work and maintaining standards. Being detail orientated
- Completing tasks and projects on time
- Acting as a positive role model for others
- Enthusiastic and optimistic about work and the future
- Look, speak and dress accordingly to maintain an image of someone who takes pride in their professional behaviour and appearance

I would now like to select a couple of these facets for further discussion.

Standards and self-accountability

We all work in a high quality regulated system. In moments of distraction or stress it can be all too easy to release work that may have required further consideration and validation. It is important that we all take some self-accountability for maintaining the standards we know are required in our daily essential service. Take time to remember that every patient you test is someone's mother, father, husband wife, sibling or friend. Take the care you would expect and give if it was for one of your family. Message: take self-accountability for your actions and maintain your standards.

Expertise

Medical laboratory science in recent times has the reputation of being the hidden service tucked away from the main stream hospitals, surgeries and patients. Our main point of contact is commonly through our phlebotomists rather than scientists and technicians – although I acknowledge there are exceptions.

We all have significant expertise in our own field and I encourage you to engage more with the physicians and health providers. You are the experts, contact them when you find a significant abnormality that may help them with the diagnosis. Listen to their needs, observe any apparent patterns in unnecessary testing and offer them a value added service with interpretation of results. At times I felt we were guilty of providing the service we believe they wanted rather than listen to their needs. The truth is often somewhere in between.

Challenge: Engage with your clinicians and health providers to deliver a value added service for your customers. Engagement is the important thing here, this will subsequently also raise the profile of the laboratory service.

On a lighter note of professionalism, in my early working years we were expected to wear a tie at work as part of the dress code and I also remember that the UK Institute organised a presentation to local Branch representatives on dress and image, even down to how to wear a tie correctly. This probably explains my want to continue wearing a tie throughout my career; it became part of my uniform and a sign to me that I was in professional work mode. It was therefore fitting that my farewell morning tea was called "Goodbye to the Tie".

As previously stated, I have always had a strong connection and involvement with our professional bodies. I should like to take a moment here a plea to you all to consider becoming more involved with our professional body, the NZIMLS. Working on Council is a very rewarding experience and it is also good to give something back to the profession. I would also encourage you all to engage with your regional representative with any issues you encounter that affect the profession. The NZIMLS head office is ably managed and the elected Council oversee the direction, finances and business matters. However, it is you the membership that are the Institute. If you don't relate your thoughts and issues to your representatives, then Council will not be able to represent you with a balanced view from the membership when making decisions that affect the future of the profession.

Whilst pleading for more involvement, my final topic is concerning training and enabling staff to perform.

Enable/train others

When people are unsure how to perform critical tasks they may be reluctant to exercise their judgment or help out. Creating a positive environment of learning and support is vital in developing a functioning team with high levels of cooperation. One of the significant results of an empowered team is a high quality service.

Throughout my career I always enjoyed training staff gaining an adult teaching qualification en route. In my latter years seeing young staff grow and develop their skills was one of the most satisfying aspects of my job. With the increase in demand for training students and new staff I have noticed an increase in what I term "training fatigue" where reluctance to find time to train has become more common, it is all too often left to the willing few. Although somewhat understandable, this is a necessary and important function of our work. You all have knowledge and skills to share, spread the load and play your part in the training and development of our future workforce, as those before did for you. The contradictory position of not having time to train because we are too busy and need help with our workload is a conundrum but clearly training and developing people is the only way to solve the problem.

We are now seeing the millennials enter the system, with an interesting change in skill sets. The millennials come very IT and tech savvy with amazing social media skills, but they still require nurturing from the long serving qualified staff that have the knowledge and expertise that comes from experience. I would urge you all to embrace them, assist in their training and let them fly under your supervision. (Note that there is also a message to millennials for the reverse.) When you invest in people you invest in the future.

Lastly, on the subject of the future:

Decisions in the future

The only thing constant in health services is change, and there are no icons, geniuses or mavericks riding over the horizon to rescue us. Yes, there will be those who champion the cause and stand to lead us through our challenges but it through a collective effort from us all doing our bit that we can lead our profession into the future. Don't sit back and let it happen. Over the coming years you will all face many workplace and personal challenges whether directed via government initiatives, from your DHBs, your laboratory management team or colleagues.

My main message today is to ask you to rediscover your passion, your reason to care, review your core values and consider whether you are being true to them. Richard Barrett, a well-known values and culture author notes: "*When a situation arises that we have to deal with, there are three different ways we can arrive at a decision on what to do: we can use our beliefs to formulate a response, we can use our values to formulate a response, or we can you our intuition to formulate a response*."

If you base decisions on your beliefs, your decisions will reflect your past history. Alternatively, if you choose to use your values to make decisions they will align with the future you want to experience (4). Today I'm asking you to be brave enough to utilise your particular strengths to be the change that is required in your workplace, regardless of your role in the laboratory. Your values and attributes can make a difference.

The next time you are involved in decision making will it be based on your beliefs or values? Take some responsibility for your future and that of the profession - show your true colours and stand up for your values when challenged. I will leave you with a quote from Viktor Frankl, the Austrian neurologist and psychiatrist as well as Holocaust survivor: *"The one thing you can't take away from me is the way I choose to respond to what you do to me. The last of one's freedoms is to choose one's attitude in any given circumstance."*

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REFERENCES

1. Kouzes J, Posner B. The Leadership Challenge. (5th Edition), Wiley, USA. 2012: 49-51.
2. VIA Character Strengths survey. Available at: http://www.viacharacter.org/www/Character-Strengths
3. Dean K W. Values-based leadership: how our personal values impact the workplace. *The Journal of Values-Based Leadership* 2008; 1 (Issue 1) Article 9. Available at: https://scholar.valpo.edu/jvbl/vol1/iss1/9
4. Barrett, R. Values-Based Leadership. Available at: http://teamperformanceus.com/wp-content/uploads/2012/11/Values-Based-Leadership.pdf

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ORIGINAL ARTICLE

Conformity evaluation checklists of API 20 E for ISO 15189:2012 internal auditing: an optimisation tool for medical laboratories

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ABSTRACT

Objectives: The purpose of this study was to develop an applied tool based on conformance requirements identified in ISO 15189:2012, which can be used by internal auditors to audit the conformity status of the use of API 20 E. The objectives include the identification of relevant conformance requirements in Clauses 4 and 5 of ISO 15189:2012 relating to areas of audit and the development of API 20 E conformity evaluation checklists for internal auditing.

Methods: The relevant conformance requirements were identified in Clauses 4 and 5 of ISO 15189:2012 by conducting content analysis. The conformance requirements were used as specific audit criteria for API 20 E conformity evaluation checklists for reagents, strip and reference equipment.

Results: Selected conformance requirements (n = 22) in Clauses 4 and 5 of ISO 15189:2012 were used to develop API 20 E conformity evaluation checklists (n = 6) and an interpretation checklist. The main advantage internal auditors gain by using such tools is the ability to produce documented assurance that medical laboratories using API 20 E routinely are competently meeting the relevant conformance requirements specified in ISO 15189:2012.

Conclusions: The present study contributes to existing knowledge of conformity management by providing internal auditors with a reasonably practical tool to conduct comprehensive and in-depth assessments of conformity status of the use of API 20 E in accordance with ISO 15189:2012 in the areas of acceptance testings as well as calibration and metrological traceability.

Key words: clinical competence, quality control, quality improvement, total quality management.

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INTRODUCTION

The medical laboratory plays an important role in providing key diagnostic information that contributes to treatment of pathological conditions. One of its capabilities is to provide diagnostic information relating to infectious conditions caused by pathogenic microorganisms. Recently, the International Organization for Standardization (ISO) has published relevant international standards to support the medical laboratory quality management system (QMS) by ensuring the processes involved are meeting rigorous management system standard (MSS) requirements. One such MSS is ISO 15189:2012 entitled 'Medical laboratories — Requirements for quality and competence' (1). ISO 15189:2012 has been specifically developed for medical laboratories to implement (2,3), and it has been developed to support the accreditation process and structured as a process-based QMS (4).

One way for medical laboratories to monitor whether processes are running effectively is to conduct audits internally on a scheduled basis. More specifically, Subclause 4.14.1 (General) of ISO 15189:2012 (1,p.16) requires medical laboratories to determine whether QMS-related processes are effectively implemented. The approach to fulfilling such requirements needs to be innovative and facilitate timely decision-making based on valid audit criteria (5). Overall, effective internal audits are essential to ensure all activities relating to the QMS are performing as per specifications of the medical laboratory.

The aim of this paper is to develop an applied tool that can be used by medical laboratories to audit the conformity status of the use of API 20 E. The specific areas of audit include documented information management in acceptance testings as well as calibration and metrological traceability of API 20 E reagents, API 20 E strip and reference equipment. This paper begins by locating the CRs relevant to the areas of audit in Clauses 4 (Management requirements) and 5 (Technical requirements) of ISO 15189:2012 (1,pp.6-39). The CRs were quantified as previously described (9). CR-specific checklists for conformity evaluation were developed, and the overall results were then summarised on a final interpretation checklist. The checklists have been designed to ensure that medical laboratories using API 20 E to detect pathogenic microorganisms are competently meeting the relevant CRs specified in ISO 15189:2012.

MATERIALS AND METHODS

Quantitative analysis of conformance requirements for the conformity evaluation of API 20 E

To establish specific audit criteria that could be performed against, relevant CRs pertaining to the conformity evaluation of API 20 E reagents (10), API 20 E strip (11) and reference equipment in ISO 15189:2012 published by the ISO were identified. Textual analysis was used to identify occurrences of CRs, as previously described (9).

Selection of graphical symbols for use in the development of API 20 E conformity evaluation checklists

Relevant graphical symbols were selected from ISO 7000:2014 entitled 'Graphical symbols for use on equipment — Registered

symbols' (12) to transmit information independently of language in the development of API 20 E conformity evaluation checklists. Although the symbols were primarily designed for use on equipment, they can still convey meaningful information to medical laboratory professionals. The date format positioned adjacent to the date graphical symbol is presented in extended format in complete representation of a calendar date as specified in ISO 8601:2004 entitled 'Data elements and interchange formats — Information interchange — Representation of dates and times' (13).

Development of API 20 E conformity evaluation checklists for reagents

The API 20 E strip contains biochemical reactions that require the use of API 20 E reagents (*n* = 6) to support the examination processes that have critical influence on the examination performance. The performance of the API 20 E reagents is required to be verified before use in examinations as specified in Subclause 5.2.3.3 (Reagents and comsumables — Acceptance testing) of ISO 15189:2012 (1,p.26). More specifically, relevant information, including lot number and expiry date, can be obtained from records, if maintained as specified in Subclause 5.3.2.7 (Reagents and consumables — Records) of ISO 15189:2012 (1,p.26). Overall, verification status and date of verification can be traced through the reagent records, depending on availability.

Development of API 20 E conformity evaluation checklists for strip

The API 20 E strip that contains biochemical reactions requires verification to ensure quality of examination results as specified in Subclause 5.6.1 (General) of ISO 15189:2012 (1,p.33). The performance of the API 20 E strip needs to be verified with suitable quality control materials. More specifically, relevant information can be obtained from records, if maintained as specified in Subclause 5.3.2.7 of ISO 15189:2012. Overall, verification status and date of verification can be traced through the reagent records, depending on availability.

Development of API 20 E conformity evaluation checklists for reference equipment

The API 20 E requires the use of a thermometer and timers to support the examination process. They need to be calibrated as specified in Subclause 5.3.1.4 (Equipment calibration and metrological traceability) of ISO 15189:2012 (1,p.24). The calibration status can be derived by obtaining the serial number as specified in Subclause 5.3.1.7 (Equipment records) of ISO 15189:2012 (1,p.25). The use of a thermometer is required to ensure the examination is performed within intended specifications as per Subclause 5.6.1 of ISO 15189:2012. The information should be expressed in degrees Celsius (°C) as specified in Clause 3 (Names, symbols, and definitions) of ISO 80000-5:2007 (14,p.3) to align with manufacturer's instructions. In addition, the use of various timers is required to ensure the duration of chemical reactions is within specified time intervals (15). Relevant information can be obtained from records, if maintained as specified in Subclause 5.3.1.7 of ISO 15189:2012. Overall, the calibration status and date of calibration can be found in the reference equipment records, depending on their availability.

Limitations of the API 20 E conformity evaluation

The API 20 E conformity evaluation process was subject to two main limitations. The first limitation was that only the materials and reagents that are incorporated into the API 20 E strips were included in the development of API 20 E conformity evaluation checklists. Two possible additional tests that are not incorporated into the API 20 E strip were excluded: reactivity of glucose fermentation metabolism using the API OF Medium and motility of facultative anaerobic bacteria using the API M Medium. The second limitation was that the internal auditor requires a minimal working knowledge on the usage of API 20 E and reference equipment. It is unreasonable to expect medical laboratory professionals from other specialities with limited exposure to the usage of API 20 E to use API 20 E conformity evaluation checklists for internal auditing and highly likely to generate misinterpretation issues (16).

RESULTS

Quantitation of conformance requirements for the conformity evaluation of API 20 E

Content analysis was used to locate relevant CRs in Clauses 4 and 5 of ISO 15189:2012 that pertain to the conformity evaluation of API 20 E. The total sum of CRs in Clauses 4 and 5 of ISO 15189:2012 was quantified (*n* = 1515) and the specific subclauses of interest are Subclauses 4.13 (Control of records) (1,pp.15-16), 5.3.1.2 (Equipment acceptance testing) (1,p.23), 5.3.1.4, 5.3.1.7, 5.3.2.3, 5.3.2.7 and 5.6.1 of ISO 15189:2012. Selected CRs of interest (*n* = 22) were used for the conformity evaluation (Table 1).

API 20 E conformity evaluation checklists graphical symbols

Graphical symbols (*n* = 10) were selected to support the transmission of information in checklists (Table 2). These symbols are widely used in medical laboratories and the descriptions were extracted from ISO 7000:2014 for reference (Table 2).

API 20 E conformity evaluation checklists for reagents

The API 20 E conformity evaluation checklists for reagents were developed based primarily on the CR (*n* = 1) of Subclause 5.3.2.3 of ISO 15189:2012 in acceptance testing (published as supplementary information in Figures S1 and S2). The first checklist evaluated the API 20 E reagents (*n* = 4) that can be verified by using commercially available quality control kits (Figure S1). The second checklist evaluated the API 20 E reagents (*n* = 2) that require organisational procedures for the verification (Figure S2).

API 20 E conformity evaluation checklists for strip

The API 20 E strip conformity evaluation checklist was developed based primarily on the CR (*n* = 1) of Subclause 5.3.2.3 of ISO 15189:2012 in acceptance testing (published as supplementary information in Figures S3 to S6). These checklists require the use of suitable quality control materials for examination in a manner close to patient specimens, as specified in Subclause 5.6.2.2 (Quality control materials) of ISO 15189:2012 (1,p.33). The first checklist evaluated biochemical tests (*n* = 11) that can be interpreted following treatment within specified conditions [(34 °C to 38 °C) and (18 h to 24 h)] (Figure S3). The second checklist evaluated biochemical tests (*n* = 5) that require an additional application of the API 20 E reagent (Mineral Oil) before treatment within specified conditions [(34 °C to 38 °C) and (18 h to 24 h)] (Figure S4). The third checklist evaluated biochemical tests (*n* = 3) requiring additional application of the API 20 E reagents (JAMES, TDA as well as VP 1 and VP 2) following treatment within specified conditions of incubation and duration (Figure S5). The fourth checklist evaluated biochemical tests (*n* = 3) requiring additional applications of the API 20 E reagents (NIT 1 and NIT 2 as well as Zn) after treatment within specified conditions of incubation and duration (Figure S6).

Table 1. The frequency of conformance requirements relating to the API 20 E conformity evaluation. Selected conformance requirements (*n* = 22) pertaining to the use of API 20 E were used for the evaluation.

ISO 15189:2012	Relevant contents	Frequency
Reagents and tests		
Subclause 4.13	*Records shall be created concurently with performance of each activity that affects the quality of the examination.*	*n* = 2
Subclause 5.3.2.3	*Consumables that can affect the quality of examinations shall be verified for performance before use in examinations.*	*n* = 2
Subclause 5.3.2.7 *	*Records shall bemaintained for each reagent and consumable that contributes to the performance of examinations.* *a) identity of the reagent or consumable;* *b) manufacturer's name and batch code or lot number;* *d) date of receiving, the expiry date, date of entering into service and, where applicable, the date the material was taken out of services;*	*n* = 12
	SUBTOTAL	***n* = 16**
Reference equipment		
Subclause 4.13	*Records shall be created concurently with performance of each activity that affects the quality of the examination.*	*n* = 1
Subclause 5.3.1.2	*Each item of equipment shall be uniquely labelled, marked or otherwise identified.*	*n* = 1
Subclause 5.3.1.4	*Metrological traceability shall be to a reference material or reference procedure of the higher metrological order available.*	*n* = 1
Subclause 5.3.1.7 †	*Records shall bemaintained for each item of equipment that contributes to the performance of examinations.* *a) manufacturer's name, model and serial number or other unique identification;*	*n* = 2
Subclause 5.6.1	*The laboratory shall ensure the quality of examinations by performing them under defined conditions.*	*n* = 1
	SUBTOTAL	***n* = 6**
	TOTAL	***n* = 22**

*Subclause 5.3.2.7 d) of ISO 15189:2012 requires the evaluation of the expiry date only.
† Subclause 5.3.1.7 b) of ISO 15189:2012 requires the evaluation of serial number only.

API 20 E conformity evaluation checklists for reference equipment

The API 20 E conformity evaluation checklists for reference equipment were developed based primarily on the CR (*n* = 1) of Subclause 5.3.1.4 of ISO 15189:2012 (published as supplementary information in Figures S3 to S6). The first checklist evaluated treatments with specified duration (18 h to 24 h) (Figures S3 and S4). The third checklist evaluated treatment within specified conditions [(18 h to 24 h) and (≥ 10 min)] (Figure S5). The fourth checklist evaluated treatment withing specified conditions [(18 h to 24 h), (2 min to 5 min) and (≥ 5 min)] (Figure S6).

Summary of results for API 20 E conformity evaluation checklists

The results were summarised according to the acceptability of API 20 E conformity evaluation checklists (Figures S1 to S6). The summary of results can be presented in a final interpretation checklist (published as supplementary information in Figure S7).

DISCUSSION

The present study was designed to develop an applied tool for the medical laboratory to audit the conformity status of the use of API 20 E in accordance with the relevant CRs in the areas of acceptance testings as well as calibration and metrological traceability in Clauses 4 and 5 of ISO 15189:2012. The design was based on the concept that the medical laboratory must do what is reasonably practicable to ensure the proper conformity required for the implementation of all related CRs. Relevant CRs (Table 1) were used to develop API 20 E conformity evaluation checklists (Figures S1 to S7). The API 20 E conformity evaluation checklists have the potential to enhance the effectiveness of operational optimisation in medical laboratories (17) as an internal audit process as specified in Subclause 4.14.1 of ISO 15189:2012 and a continual improvement process as specified in Subclause 4.12 (Continual improvement) of ISO 15189:2012 (1,pp.14-15).

Table 2. Descriptions of graphical symbols. The selected graphical symbols and descriptions are extracted from ISO 7000:2014. The symbols were used in the API 20 E conformity evaluation checklists to support interpretation.

Symbols	Definitions
	**Batch code** To identify the manufacturer's batch or lot code
	**Catalogue number** To identify the manufacturer's catalogue number
	**Date** To identify the control which sets and indicates the date
	**Negative control** To identify material that is used as a negative control to be part of the quality control procedure
	**Person identification** To identify the control or the indicator to enter or call up personal data for identification
	**Positive control** To identify material that is used as a positive control to be part of the quality control procedure
	**Programmable start** To identify the control of a programmable timer to start an operation at a specific point in time or after a specific duration; or to identify a display of the programmed or to-be-programmed start time
	**Serial number** To identify the manufacturer's serial number
	**Temperature limit** To indicate the maximum and minimum temperature limits at which the item shall be stored, transported or used
	**Use by date** To indicate that the device should not be used after the date accommpanying the symbol

The main aim of the development of API 20 E conformity evaluation checklists is to offer comprehensive coverage of all relevant CRs associated with the use of API 20 E. The design was primarily for acceptance testing; however, it can equally be used for the audit of verification as specified in Subclause 5.6.2.1 (General) of ISO 15189:2012 (1,p.33), assuming that the same verification procedure is used for both processes. The proposed checklists provide a structured approach for the internal auditor to conduct audit and improvement activities with an appropriate level of scientific certainty. While there are no applicable requirements for the appointment of an internal auditor, it is safe to assume that the appointee should have received effective training in assessing the performance of processes of the QMS. The selected internal auditor should also be able to maintain impartiality (18) and objectivity (19), as specified in Subclause 4.14.5 (Internal audit) of ISO 15189:2012 (1,p.17). Nevertheless, this can become paradoxical because the selection restriction that auditors must be medical laboratory professionals who are independent of the activity is highly likely to hinder the audit productivity. With this notion in mind, it is important for medical laboratories to take innovative steps to maximise suitability of ways to conduct internal audits (5,20).

Comprehensiveness coverage was based on the notion that all activities in the medical laboratory QMS are fulfilled and subject to the right mix of technical expertise and audit rigour to provide robust and scientific assurance to laboratory management. It is important to note the term 'all activities in the quality management system' as specified in Subclause 4.14.5 of ISO 15189:2012 should be treated as a '100 % inspection'; the term has been defined by the ISO as 'inspection of selected characteristic(s) of every item in the group under consideration' in Subclause 4.1.5 of ISO 3534-2:2006 (21,p.65). The 'selected characteristic(s) of every item' should be the CRs in Clauses 4 and 5 of ISO 15189:2012. A total of 1515 CRs has been identified in Clauses 4 and 5 of ISO 15189:2012 (9) and internal audits need to be performed to determine whether all activities in the QMS conform to these CRs (3,22,23). Overall, the use of API 20 E conformity evaluation checklists has the potential to competently address the internal audit validity.

The use of API 20 E conformity evaluation checklists has three technical considerations that need to be applied by the internal auditor. First, environmental illumination condition may play a factor in the interpretation of API 20 E results. While there are no specific CRs prescribing what the illumination level should

be, it is stated that illumination level needs to be controlled if it adversely affects the required quality of examination as specified in Subclause 5.2.6 (Facility maintenance and environmental conditions) of ISO 15189:2012 (1,p.23). The illumination factor should be considered by the internal auditor if it adversely influences the medical laboratory (24) and further guidance can be sought from ISO 8995-1:2002 entitled 'Lighting of work places — Part 1: indoor' (25) and ISO 8995-1:2002/Cor.1:2005 entitled 'Lighting of work places — Part 1: indoor — Technical corrigendum 1' (26). Second, the internal auditor should check that the reference equipment is calibrated by a facility that has achieved accreditation to ISO/IEC 17025:2017 entitled 'General requirements for the competence of testing and calibration laboratories' (27) or by an in-house facility capable of producing acceptable equivalent results. Third, the internal auditor should know that it is a CR that records are created for each activity that affects the quality of the examination, as specified in Subclause 4.13 of ISO 15189:2012. Records of the API 20 E reagents, API 20 E strip and reference equipment that contribute to the performance of examinations must be readily available as specified in Subclauses 5.3.1.7 and 5.3.2.7 of ISO 15189:2012. Further guidance can be sought from ISO 15489-1:2016 entitled 'Information and documentation — Records management — Part 1: concepts and principles' (28).

In relation to the final interpretation of results of API 20 E conformity evaluation checklists, there are two considerations that the internal auditors need to address concerning possible interpretation bias. First, the internal auditor needs to ensure that all activities relating to the use of API 20 E fulfil both CRs of ISO 15189:2012 as well as CRs established by the medical laboratory, as specified in Subclause 4.14.5 a) of ISO 15189:2012 (1,p.17). The second potential for bias in for interpretation relates to the determination of effectiveness status by the internal auditor. This is a CR as specified in Subclause 4.14.5 b) of ISO 15189:2012 (1,p.17). It is important to note that the term 'effectiveness' has been defined by the ISO as 'extent to which planned activities are realized and planned results are achieved' in Subclause 3.7.11 of ISO 9000:2015 (29,p.22) and differs from 'appropriateness' and 'efficiency'. The term 'appropriateness' has been defined by the ISO as 'suitability of any given indicator for evaluating a specific activity' in Subclause 2.5 of ISO 11620:2014 (30,p.2) and 'efficiency' has been defined by the ISO as 'relationship between the result achieved and the resources used' in Subclause 3.7.10 of ISO 9000:2015 (29,p.22). The internal audit process needs to ensure it has assessed the effectiveness status of all activities in the QMS.

CONCLUSIONS

The present study was undertaken to develop practical work documents for the medical laboratory to conduct internal audits to ensure practices relating to the use of API 20 E are conforming to the relevant CRs of ISO 15189:2012. The results of this research have two positive practical implications when used by internal auditors. First, the developed API 20 E conformity evaluation checklists allow internal auditors to determine whether the practices of the medical laboratory are meeting the specifications of ISO 15189:2012. Second, the internal auditors can use the results for continual improvement purposes in case of shortfalls. Overall, the API 20 E conformity evaluation checklists have been developed to support internal auditors in ensuring the practices relating to API 20 E are competently meeting the relevant CRs specified in ISO 15189:2012. A natural progression of this work is to encourage medical laboratory professionals to develop further reasonably practicable documents for internal audit for in-service test kits that are being used by the medical laboratory.

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REFERENCES

1. International Organization for Standardization. Medical laboratories — Requirements for quality and competence. 3rd edn. ISO 15189:2012. International Organization for Standardization, Geneva, 2014.
2. Mok D, Ang E. ISO 15189:2012 implementation: an update of related international standards and guidance documents for medical laboratory quality management. *N Z J Med Lab Sci* 2016; 70: 42-66.
3. Mok D, Lim E, Eckersley K, Hristov L, Kirsch C. ISO 15189:2012 implementation: an applied guide for medical laboratories. *Aust J Med Sci* 2013; 34: 134-173.
4. Mok D. ISO 15189:2012 implementation checklists for conformity assessment by accreditation bodies: a comparative analysis. *N Z J Med Lab Sci* 2017; 71: 84-99.
5. Blind K. The impact of standardisation and standards on innovation. In: Edler J, Cunningham P, Gök A, Shapira P, eds. Handbook of Innovation Policy Impact. Eu-SPRI Forum on Science, Technology and Innovation Policy. Edward Elgar Publishing, Cheltenham, 2016: 423-449.
6. International Organization for Standardization. Guidelines for Auditing Management Systems. 3rd edn. ISO 19011:2018. International Organization for Standardization, Geneva, 2018.
7. Mok D, Chowdhury S. Document review checklists for ISO 15189:2012 internal auditing: an applied tool for medical laboratories. *Aust J Med Sci* 2016; 37: 48-55.
8. Mok D, Nabulsi R, Chowdhury S. Document review checklists for ISO 22870:2016 internal auditing: an applied tool for medical laboratories. *N Z J Med Lab Sci* 2018; 72: 59-64.
9. Mok D, Lim E, Bingham A. Identification of ISO 15189:2012 conformance requirements for medical laboratory internal auditing. *Aust J Med Sci* 2015; 36: 2-14.
10. bioMérieux. Reagents. bioMérieux, Marcy-l'Étoile, 2015.
11. bioMérieux. API® 20 E™. bioMérieux, Marcy-l'Étoile, 2010.
12. International Organization for Standardization. Graphical Symbols for Use on Equipment — Registered Symbols. 5th edn. ISO 7000:2014. International Organization for Standardization, Geneva, 2014.

13. International Organization for Standardization. Data Elements and Interchange Formats — Information Interchange — Representation of Dates and Times. 3rd edn. ISO 8601:2004. International Organization for Standardization, Geneva, 2004.
14. International Organization for Standardization. Quantities and Units — Part 5: Thermodynamics. ISO 80000-5:2007. International Organization for Standardization, Geneva, 2011.
15. Lombardi MA. Time measurement. In: Webster JG, Eren H, eds. Measurement, Instrumentation, and Sensors Handbook: Electromagnetic, Optical, Radiation, Chemical, and Biomedical Measurement. 2nd edn. Electrical Engineering Handbook. Taylor & Francis Group, Boca Raton, 2014: 41-41-41-21.
16. Minami CA, Bilimoria KY, Yang AD. The science of quality improvement. In: Kelz RR, Wong SL, eds. Surgical Quality Improvement. Success in Academic Surgery. Springer Nature, Cham, 2017: 9-26.
17. Du D-Z, Pardalos PM, Wu W. History of optimization. In: Floudas CA, Pardalos PM, eds. Encyclopedia of Optimization. 2nd edn. Springer Science+Business Media, New York, 2009: 1538-1542.
18. Cullity G. Impartiality. In: LaFollette H, ed. The International Encyclopedia of Ethics. John Wiley & Sons, Hoboken, 2013: 2560-2566.
19. Mathison S. Objectivity. In: Mathison S, ed. Encyclopedia of Evaluation. SAGE Publications, Thousand Oaks, 2005: 286.
20. Cargill CF. Standardization, innovation and reality: matching theory and practice. In: Hawkins R, Blind K, Page R, eds. Handbook of Innovation and Standards. Edward Elgar Publishing, Cheltenham, 2017: 412-426.
21. International Organization for Standardization. Statistics — Vocabulary and Symbols — Part 2: Applied Statistics. 2nd edn. ISO 3534-2:2006. International Organization for Standardization, Geneva, 2006.
22. Russell J. Is your lab ready? *Biomed Sci* 2017; February: 32-33.
23. Mok D, Nabulsi R, Chowdhury S. Identification of ISO 22870:2016 conformance requirements for medical laboratory internal auditing. *N Z J Med Lab Sci* 2017; 71: 41-54.
24. Boyce PR. Illumination. In: Salvendy G, ed. Handbook of Human Factors and Ergonomics. 4th edn. John Wiley & Sons, Hoboken, 2012: 673-698.
25. International Organization for Standardization. Lighting of Work Places — Part 1: Indoor. 2nd edn. ISO 8995-1:2002. International Organization for Standardization, Geneva, 2002.
26. International Organization for Standardization. Lighting of Work Places — Part 1: Indoor — Technical Corrigendum 1. ISO 8995-1:2002/Cor.1:2005. International Organization for Standardization, Geneva, 2005.
27. International Organization for Standardization, International Electrotechnical Commission. General Requirements for the Competence of Testing and Calibration Laboratories. 3rd edn. ISO/IEC 17025:2017. International Organization for Standardization, Geneva, 2017.
28. International Organization for Standardization. Information and Documentation — Records Management — Part 1: Concepts and Principles. 2nd edn. ISO 15489-1:2016. International Organization for Standardization, Geneva, 2016.
29. International Organization for Standardization. Quality Management Systems — Fundamentals and Vocabulary. 4th edn. ISO 9000:2015. International Organization for Standardization, Geneva, 2015.
30. International Organization for Standardization. Information and Documentation — Library Performance Indicators. 3rd edn. ISO 11620:2014. International Organization for Standardization, Geneva, 2014.

This article has supplementary data as noted in the text. This is available online at http://www.nzimls.org.nz under the Journal November issue.

Dennis Mok completed his Fellowship of NZIMLS during 2018. He is pictured here receiving his Certificate from NZIMLS President, Terry Taylor during the NZIMLS 2018 Annual Scientific Meeting.

Life Membership was awarded to Tony Mace during the ASM. He is pictured here receiving his Certificate from NZIMLS President, Terry Taylor.

Life Membership was awarded to Ken Beechey during the ASM. NZIMLS President, Terry Taylor presented Ken with his Certificate during the ASM.

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GUIDELINE

The important role of the clinical microbiology laboratory in the New Zealand Antimicrobial Resistance Action Plan and detection of carbapenemase-producing Enterobacteriaceae

Juliet Elvy, on behalf of the New Zealand Antimicrobial Susceptibility Testing Committee (NZNAC)

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Antimicrobial resistance (AMR) is arguably the single biggest infectious diseases threat we currently face in New Zealand, and globally. New resistance mechanisms are emerging, which threaten our ability to treat common infectious diseases, such as urinary tract infections, and will potentially affect the ability of cancer, surgical and other services to provide safe and effective healthcare. As such, the global AMR crisis has moved to the top of government agendas worldwide. In 2011, the UK Chief Medical Officer Dame Sally Davies stated, *"Antimicrobial resistance poses a catastrophic threat. If we don't act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that can't be treated by antibiotics. And routine operations like hip replacements or organ transplants could be deadly because of the risk of infection"* (1).

In 2015, The World Health Organisation adopted a global action plan on antimicrobial resistance. This was in recognition that, *"Without harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill"* (2). New Zealand made a commitment to the World Health Assembly to have in place a national action plan on AMR by 2017. Subsequently, in December 2017, the New Zealand Ministry of Health set out the New Zealand Antimicrobial Resistance Action Plan (3).

Carbapenemase-producing Enterobacteriaceae, or CPE, harbour resistance to carbapenems such as ertapenem and meropenem, which are last line antibiotics usually reserved for serious and difficult to treat infections. Until recently in New Zealand, CPE have been mostly isolated from people with a history of overseas hospitalisation and travel to regions where CPE is now endemic, such as the Indian subcontinent and Southeast Asia. Emerging evidence now suggests that CPE infections are arising in people without prior travel history outside of New Zealand (4). This is of major concern.

Medical microbiology laboratories in New Zealand play a critical role in AMR prevention strategies, a situation acknowledged in the Ministry of Health's New Zealand Antimicrobial Resistance Action Plan. Within this plan, listed as a Year One Priority Action, is "To develop and implement an enhanced surveillance programme for multi-drug resistant gram negative micro-organisms to include laboratory identification and reporting of carbapenemase-producing *Enterobacteriaceae* (CPE)". Integral to this Priority Action is the ability of microbiology laboratories to accurately, and consistently, identify these resistance mechanisms on a day-to-day basis. This capability should not be limited to larger laboratories with access to technology and expertise in antimicrobial susceptibility testing or AMR, but rather should include every clinical microbiology laboratory across New Zealand.

We are therefore pleased to publish the New Zealand National Antimicrobial Susceptibility Testing Committee (NZNAC) CPE guideline, entitled "Minimum laboratory requirements for the detection of carbapenemase-producing Enterobacteriaceae from clinical samples and screening specimens." This document has been endorsed by the New Zealand Microbiology Network and will be included in the New Zealand CPE Action Plan, expected for publication by the Ministry of Health in 2019. IANZ have been notified about the document, and laboratories are expected to comply with the recommendations outlined within. We therefore urge all New Zealand microbiology laboratories to promptly read and implement these recommendations. Any questions or comments are gratefully received, via email to the NZNAC administrator sarah.underwood@esr.cri.nz.

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REFERENCES

1. Chief Medical Officers report 2011, available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/138331/CMO_Annual_Report_Volume_2_2011.pdf
2. World Health Organisation Global Action Plan on Antimicrobial Resistance, available at: http://www.who.int/antimicrobial-resistance/global-action-plan/en/
3. New Zealand Antimicrobial Resistance Action Plan Ministry of Health and Ministry for Primary Industries. 2017. *New Zealand Antimicrobial Resistance Action Plan. Wellington: Ministry of Health, available at:* https://www.health.govt.nz/system/files/documents/publications/new-zealand-antimicrobial-resistance-action-plan.pdf
4. ESR 2018 data: https://surv.esr.cri.nz/antimicrobial/AccqEnterobacteriaceae.php).

Minimum laboratory requirements for the detection of carbapenemase-producing Enterobacteriaceae from clinical samples and screening specimens

1 Aim

The aim of this document is to provide a minimum requirement for the laboratory detection of carbapenemase-producing Enterobacteriaceae (CPE) in New Zealand and to ensure laboratories can identify when confirmatory testing, referral of isolates, and notification to clinical and infection prevention teams is required.

2 Background

There are several different mechanisms by which Enterobacteriaceae can develop resistance to carbapenem antibiotics.

Acquired carbapenemases (carbapenem-hydrolysing enzymes) are of most concern because their genetic determinants are mainly carried on plasmids and therefore can transfer between strains, species and genera. Detection of CPE can be difficult because:

- not all carbapenem resistance is due to carbapenemase production, and
- not all carbapenemase producers are phenotypically resistant to carbapenems using standard antimicrobial susceptibility testing (AST) breakpoints.

Other mechanisms of carbapenem resistance, such as extended-spectrum beta-lactamase (ESBL) or AmpC beta-lactamase production, combined with porin loss (commonly seen in *Enterobacter* spp) or efflux mechanisms, are not readily transferable between strains. Such non-carbapenemase- producing, carbapenem-resistant Enterobacteriaceae (non-CP CRE) do not pose the same infection prevention and control risk. Laboratories must therefore be able to identify organisms with acquired carbapenemases, and differentiate them from isolates with other mechanisms of carbapenem resistance, in order to support clinicians to make appropriate treatment decisions and implement appropriate infection prevention measures. Also key to improving the patient's outcome is the timely provision of accurate susceptibility data to support directive therapy.

Laboratories should maintain a high index of suspicion for CPE, based on clinical presentation, epidemiological risk factors (such as overseas travel and hospitalisation) and susceptibility testing results. A low threshold for further confirmatory testing of suspect isolates, either locally or by referral to another laboratory, should be maintained.

This document outlines procedures required for the detection of CPE in clinical specimens (section 4) and CPE screening samples (section 5). Laboratories may need to modify their testing processes or increase their testing capacity in order to meet these standards.

3 Scope

Laboratory detection of acquired carbapenemases in Enterobacteriaceae.[1]

[1] The authors acknowledge the recent changes in taxonomy that have resulted in several genera formerly included in the family Enterobacteriaceae now being included in other families in the order Enterobacterales. However, the term Enterobacteriaceae is used in this document, but should be considered to cover all genera now included in the order Enterobacterales.

Not included

- Carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
- Organisms with intrinsic carbapenemases, such as *Stenotrophomonas maltophilia* and *Aeromonas* spp
- ESBL or AmpC beta-lactamase detection in Enterobacteriaceae
- Environmental and veterinary samples

4 Clinical isolates

4.1 Antimicrobial susceptibility testing and use of an indicator antimicrobial for CPE

All diagnostic laboratories should have the capability to perform antimicrobial susceptibility testing (AST) in accordance with methods recommended by either the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI). The most recent versions of these methods should be used.

All clinically significant Enterobacteriaceae isolates should be screened for the presence of a carbapenemase using an indicator antimicrobial as part of routine AST. Subsequent additional confirmatory testing should be performed where the indicator antibiotic indicates it is necessary.
The suggested indicator carbapenem is meropenem since it offers the best balance of sensitivity and specificity for the detection of CPE.

Recommended CPE screening method for all hospital and community specimens:

Test an indicator carbapenem (meropenem) against all clinically significant Enterobacteriaceae isolates
or
Test an indicator carbapenem (meropenem) against all clinically significant Enterobacteriaceae isolates that have decreased susceptibility to cefpodoxime, ceftriaxone or ceftazidime.
or
Test an indicator carbapenem (meropenem) against all clinically significant Enterobacteriaceae isolates that are resistant to cephalexin. This is the least specific option for detection of CPE, but may be considered where a carbapenem or third-generation cephalosporin is not tested as part of first-line AST.

Where there are epidemiological risk factors for CPE (such as overseas travel or hospitalisation, previous known CPE colonisation, or a household member with CPE), Enterobacteriaceae isolates resistant to amoxicillin-clavulanate, should also be considered for meropenem susceptibility testing.

4.1.1 Urine direct susceptibility testing

Laboratories performing direct susceptibility testing (DST) on urine samples should ensure that a valid inoculum is achieved before reading and reporting susceptibility results. Any invalid results should be repeated using a controlled inoculum to avoid inaccurate susceptibility results. This has particular relevance when reading the indicator antimicrobial zone diameters.

4.2 Indicator carbapenem interpretive criteria

Laboratories are advised to use the EUCAST carbapenemase screening criteria which offers sufficient sensitivity for CPE detection in low-prevalence settings such as New Zealand. Organism identification to species level is required for valid interpretation of AST, including CPE screening criteria.

Additional confirmatory testing (section 6) should be performed on all Enterobacteriaceae isolates where:

Meropenem MIC >0.12 mg/L
or
Meropenem disc zone diameter <25 mm
or
Meropenem disc zone diameter 25-27 mm, if also resistant to piperacillin-tazobactam (and/or temocillin)[2]

or

Automated AST system (eg, Vitek 2, Phoenix) indicates decreased susceptibility to meropenem or that a carbapenemase may be present. Note where the lowest meropenem concentration tested does not allow interpretation according to the criteria outlined above, an additional step may be required to meet these minimum standards. For example, laboratories using Vitek 2 AST should consider manual meropenem AST and/or additional confirmatory testing for isolates with meropenem MICs ≤0.25 mg/L that are also resistant to a third-generation cephalosporin and piperacillin-tazobactam. Enterobacteriaceae with reduced susceptibility to ertapenem, but remaining fully susceptible to meropenem, do not routinely require further testing for CPE.

5 CPE screening samples

Clinical selection criteria should be applied in line with local infection prevention procedures and in accordance with national CPE guidance documents.

5.1 Recommended samples

A faeces specimen or rectal swab with visible faecal material are the minimum recommended sample types for CPE screening.

Additional samples types should be considered where appropriate, in line with local and national infection prevention guidance documents:

1. Urine, if symptomatic or urinary catheter/nephrostomy/stent in situ;
2. Swab from wounds and insertion sites of invasive medical devices and catheters; and
3. Lower respiratory tract specimens, if intubated.

5.2 Laboratory methods for detection of CPE from screening samples

5.2.1 Culture-based methods

Selective culture is the most commonly used methodology for detection of CPE in screening samples. There is currently no consensus best-practice culture medium for this purpose, but the use of a commercially available, selective chromogenic media is recommended. Laboratories should note that these media vary in their performance for detection of the different types ofcarbapenemases.

Based on the epidemiology of CPE in NZ, laboratories should utilise media capable of detecting CPE with low carbapenem MICs (such as OXA-48/OXA-48-like producing isolates). This may require the utilisation of two different selective media.

MacConkey agar with a carbapenem disc is inferior to screening with chromogenic media and is not recommended as the sole screening method.

Any Enterobacteriaceae growth on CPE screening agar should have AST (including meropenem) performed followed by confirmatory testing as required (section 6).

5.2.2 Molecular methods for detection of carbapenemase genes direct from screening sample

Molecular CPE test panels currently commercially available detect the most common carbapenemase genes. Less common carbapenemase types will not be detected and therefore culture-based screening may also be required where there is high clinical suspicion for a CPE genotype not included in the molecular panel available.

Clinical samples in which CPE resistance genes are detected directly should have reflex culture performed to obtain an isolate for identification and susceptibility testing.

[2] For *Enterobacter, Serratia, Citrobacter freundii, Proteus vulgaris, Providencia and Morganella* species, the Clinical Microbiologist may exercise discretion regarding the need for further testing if resistance is likely to be due to a combination of AmpC de-repression and porin deficiency (eg, when there is no co-resistance to other antibiotic classes and resistance develops progressively during antimicrobial therapy).

6 Confirmatory testing for CPE

Confirmatory testing for the presence of carbapenemase or a carbapenemase gene may be performed locally or by referral to a second laboratory with the necessary expertise. Accurate organism identification to species level is mandatory for isolates which require CPE confirmatory testing.

Confirmatory testing for isolates from invasive infection should be regarded as urgent, with results available as soon as possible, and within 24 hours. Confirmatory testing for screening or community isolates may be considered less urgent but should still be available promptly and within 3 working days. Primary diagnostic laboratories should have agreed referral protocols in place to ensure compliance with these requirements. There are many available methods for confirmatory testing; extensive evaluation studies of the various methods have been undertaken elsewhere and are not included in this document.

6.1 Phenotypic methods

Suitable phenotypic methods include:

1. Colorimetric tests, utilising pH related colour change due to hydrolysis of the indicator carbapenem (eg, CarbaNP, BlueCarba);
2. Carbapenem inactivation method (CIM) or modified CIM (mCIM);
3. Combination disc testing (eg, MAST D70C); and
4. Immunoassays for detection of carbapenemases (eg, Resist-3 O.K.N for detection of OXA- 48-like, KPC and NDM carbapenemases).

The modified Hodge test is no longer recommended due to difficulties in interpretation, and lack of sensitivity and specificity.

Isolates with a positive phenotypic carbapenemase test will also require genotypic confirmation by a molecular method, either by local testing or referral to ESR.

Isolates with a negative phenotypic carbapenemase test but with a high clinical suspicion for CPE (due to epidemiological risk factors) may require additional testing using a molecular method.

6.2 Molecular methods

Commercially available molecular platforms detect the most common carbapenemase types which account for >95% of CPE. Since less common carbapenemase types will not be detected on these platforms, if a high suspicion for CPE remains despite a negative molecular test, a phenotypic carbapenemase test and/or referral to ESR is advisable.

7 Notification

All laboratories must have a documented procedure for notification of all suspected and confirmed CPE isolates.

For patients in a health care facility all confirmed CPE isolates must be notified as soon as possible and on the same day to:

1. The treating clinician;
2. The supervising clinical microbiologist; and
3. The Infection Prevention and Control team.

For community patients (not in a health care facility) all confirmed CPE isolates must be notified as soon as possible and on the same day to:

1. The supervising clinical microbiologist; and by the next working day to:
1. The treating clinician; and
2. The Infection Prevention and Control team.

All possible or suspected CPE isolates must be notified on the same day to the supervising clinical microbiologist whilst awaiting confirmation. Onward notification to the clinician and Infection Prevention and Control teams is at the discretion of the clinical microbiologist and should take into account the likelihood of CPE and potential clinical risk.

8 Reporting

Enterobacteriaceae isolates confirmed by molecular methods to carry a carbapenemase gene should be reported as a 'Carbapenemase-producing *Enterobacteriaceae* (CPE)'.

Carbapenem-resistant isolates with a positive phenotypic test may be reported as a 'Probable carbapenemase-producing *Enterobacteriaceae* (CPE), awaiting confirmation'

Non-carbapenemase-producing, carbapenem-resistant Enterobacteriaceae (non-CP CRE) isolates should not be reported as 'Carbapenemase-producing *Enterobacteriaceae* (CPE)' in order to maintain differentiation from CPE.

Similarly, terms such as carbapenemase-producing organism (CPO) and carbapenem-resistant organism (CRO) should not be used for confirmed carbapenemase-producing Enterobacteriaceae.

9 Referral of isolates to ESR

All suspected or confirmed CPE isolates should be referred to ESR's Antimicrobial Reference Laboratory, Kenepuru, Porirua, for confirmation and typing, as follows:

1. All isolates confirmed as CPE using a molecular method;
2. Enterobacteriaceae isolates with a positive phenotypic carbapenemase test, but confirmatory molecular testing is negative or not done; and
3. Enterobacteriaceae isolates with decreased carbapenem susceptibility from patients with risk factors for CPE, but isolate negative in phenotypic carbapenemase test and molecular test (if done).

Isolates do not require referral to ESR where there is a low index of suspicion and the carbapenemase confirmatory test is negative, such as AmpC beta-lactamase-producing Enterobacteriaceae (eg, *Enterobacter*,) with decreased susceptibility to meropenem and/or ertapenem.
When isolates are referred to ESR for confirmation, the following information should be supplied in addition to that requested on the standard ESR referral form (see http://www.esr.cri.nz/assets/Test-Forms/ESR0039-Single-Human-Source-Specimen.pdf):

Based on the epidemiology of CPE in NZ, laboratories should utilise media capable of detecting CPE with low carbapenem MICs (such as OXA-48/OXA-48-like producing isolates). This may require the utilisation of two different selective media.

MacConkey agar with a carbapenem disc is inferior to screening with chromogenic media and is not recommended as the sole screening method.

Any Enterobacteriaceae growth on CPE screening agar should have AST (including meropenem) performed followed by confirmatory testing as required (section 6).

1. Full antimicrobial susceptibility test results for the isolate, including printout from Vitek or similar if available; and
2. Risk factor information, in particular any details of recent overseas travel and hospitalisation for the patient or close household contacts; and
3. Molecular testing results (if available).

ESR should aim to confirm the isolate is a CPE within 3 working days of receipt. Any positive results should be reported to the referring laboratory as soon as possible and on the same day that results are available.

10 Storage of isolates

All confirmed CPE isolates will be stored by ESR on referral. Primary diagnostic laboratories are also advised to store isolates for surveillance purposes for a minimum of 6 months.

11 Carbapenemases in non-Enterobacteriaceae

Detection of carbapenemases in non-Enterobacteriaceae isolates is beyond the scope of this document. However, laboratories must be aware that transferable carbapenemases do also occur in species such as *P. aeruginosa* and *A. baumannii*. As such, laboratories are advised to follow EUCAST or CLSI guidance to determine when further confirmatory testing or referral to ESR should be performed.

References

CDC. Facility guidance for control of carbapenem-resistant Enterobacteriaceae (CRE). Atlanta (GA): Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases; 2015. Available at: https://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html. Last accessed 6 March 2018.

EUCAST. EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. Version 2.0; 2017 Jul. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_170711.pdf. Last accessed 6 March 2018.

Fattouh R, Tijet N, McGeer A, Poutanen SM, Melano RG, Patel SN. What is the appropriate meropenem MIC for screening of carbapenemase-producing Enterobacteriaceae in low-prevalence settings? Antimicrob Agents Chemother 2016; 60: 1556–9.

Health Protection Scotland. Toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae in Scottish acute settings. Health Protection Scotland. Version 1.1; 2017 Jul. Available at: http://www.hps.scot.nhs.uk/resourcedocument.aspx?id=6083. Last accessed 6 March 2018.

Parker VA, Logan CK, Currie B. Carbapenem-resistant Enterobacteriaceae (CRE) control and prevention toolkit. Rockville (MD): Dept. of Health and Human Services (US), Agency for Healthcare Research and Quality; 2014 Apr. AHRQ Publication No. 14-0028.

Pierce VM, et al. Modified carbapenem inactivation method for phenotypic detection of carbapenemase production among Enterobacteriaceae. J Clin Microbiol 2017; 55: 2321-33.

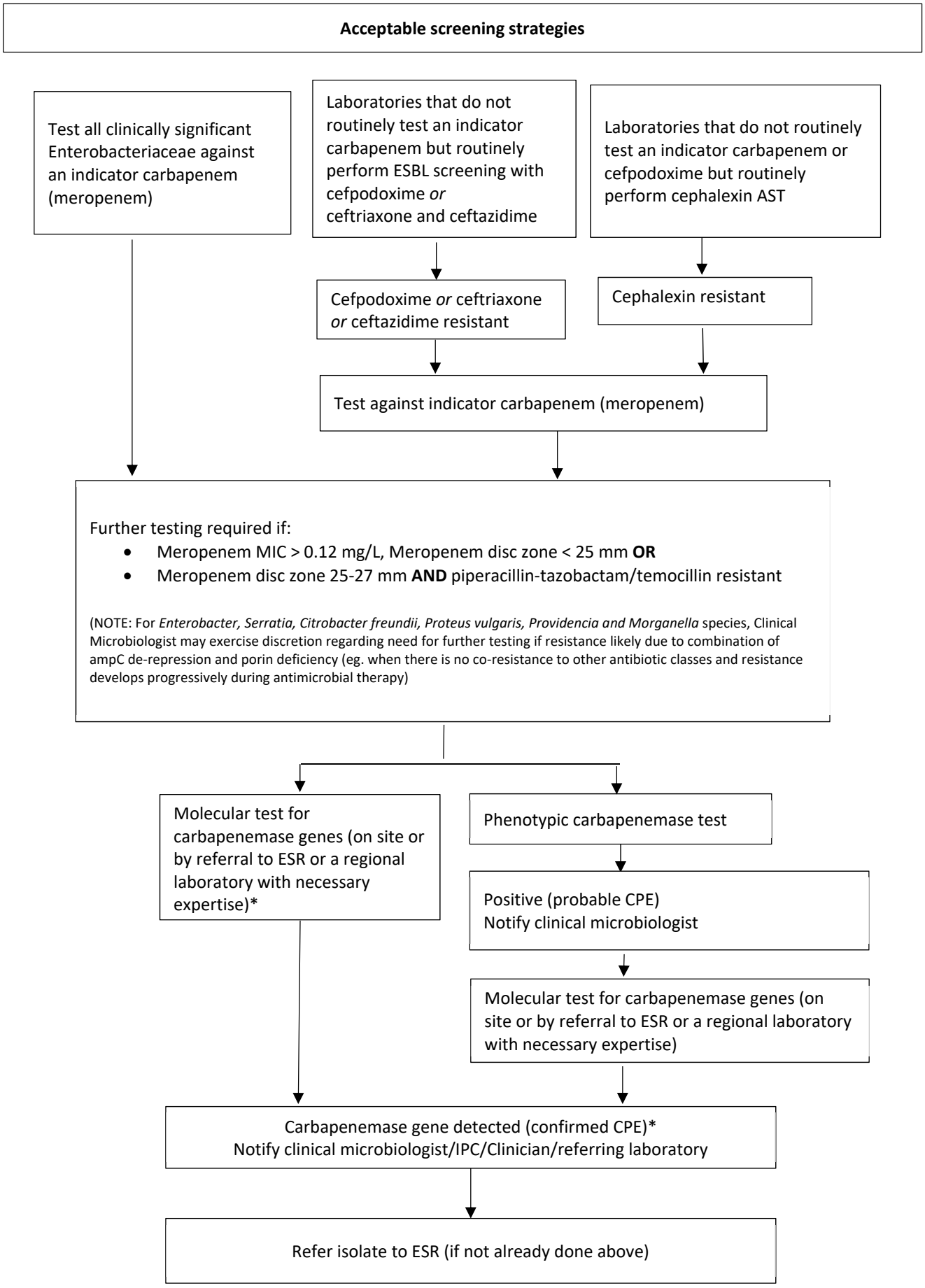
Public Health England. Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae. London: Public Health England; 2013. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/329227/Acute_trust_toolkit_for_the_early_detection.pdf. Last accessed 6 March 2018.

Public Health England. UK standards for microbiology investigations. Laboratory detection and reporting of bacteria with carbapenem-hydrolysing β-lactamases (carbapenemases). London: Public Health England; 2014. Available at: http://webarchive.nationalarchives.gov.uk/20140714032104/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317138520481. Last accessed 6 March 2018.

State Government of Victoria. Victorian guideline on carbapenemase-producing Enterobacteriaceae. Version 2. Victoria, Australia: State of Victoria, Department of Health and Human Services; 2017 Apr. Available at: https://www2.health.vic.gov.au/public-health/infectious-diseases/infection-control-guidelines/carbapenemase-producing-enterobacteriaceae-management. Last accessed 6 March 2018.

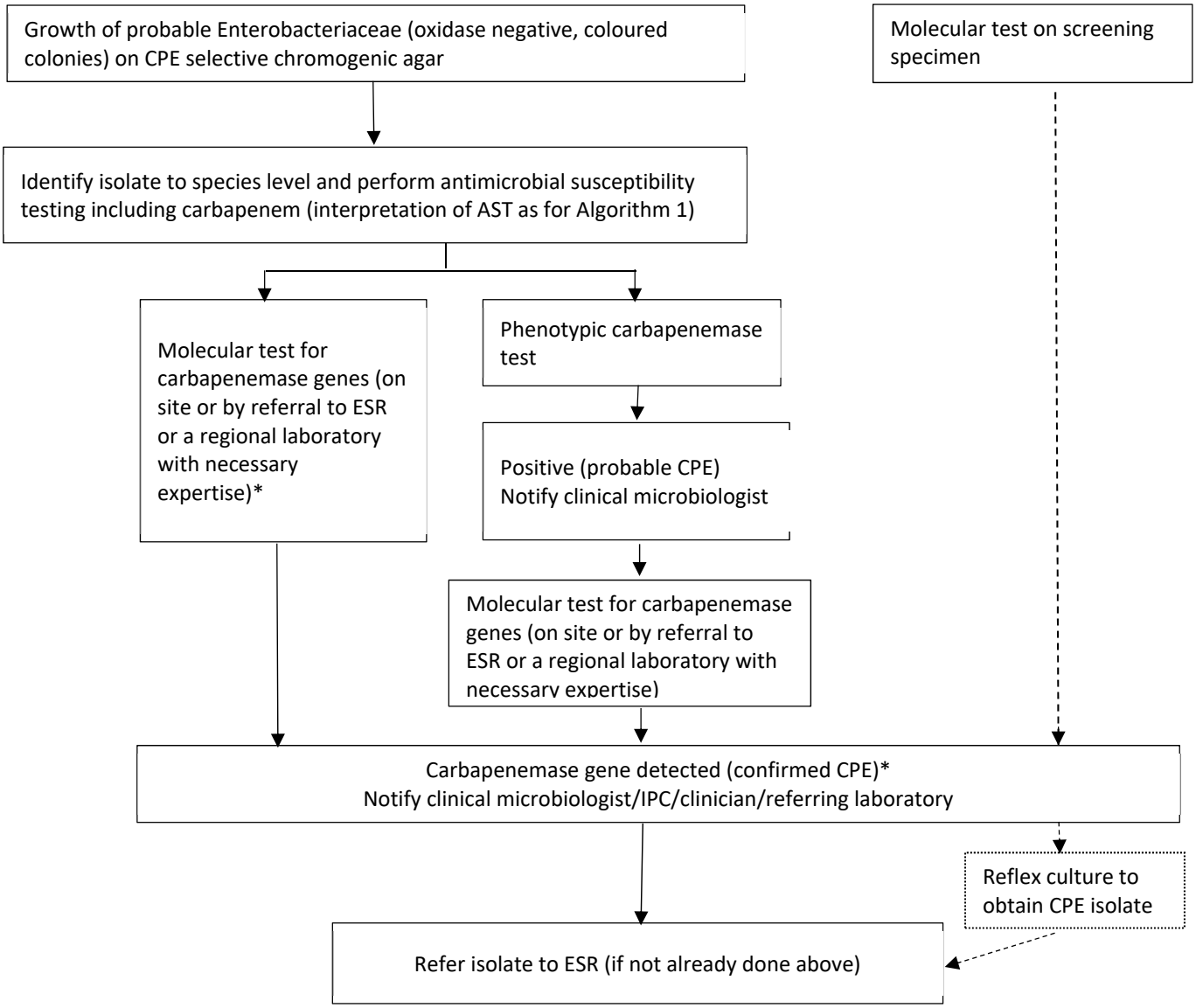
Tzouvelekis LS, et al. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. Clin Micro Rev 2012; 25: 682-707.

Algorithm 1. Clinical specimens



*phenotypic carbapenemase test or referral to ESR may still be required if molecular test negative but significant clinical suspicion for CPE type not included in molecular assay

Algorithm 2. Screening specimens



*phenotypic carbapenemase test or referral to ESR may still be required if molecular test negative but significant clinical suspicion for CPE type not included in molecular assay

CASE STUDY

Fine needle aspiration cytology of pulmonary papillary adeno-carcinoma mimicking papillary thyroid carcinoma

Sharda Lallu, Sarla Naran and Peter Bethwaite

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ABSTRACT

We report a case of primary pulmonary papillary adenocarcinoma demonstrating classic nuclear and architectural features of papillary thyroid carcinoma including nuclear pseudo-inclusions, intranuclear grooves in the tumour cells nuclei, ground glass nuclei, papillary architecture with true fibrovascular cores lined by cuboidal cells with oval nuclei. Immunohistochemical staining was performed on cell block and the preparations showing the lesional cells to be positive for TTF-1, Napsin A and negative for Thyroglobulin and PAX8. The appearances and immunophenotype were consistent with a primary pulmonary papillary adenocarcinoma and excluded a metastasis from the thyroid. Awareness of the existence of PTC- like pulmonary papillary carcinoma along with use of immunohistochemistry can avoid misdiagnosis or unnecessary clinical and radiologic investigation.
Keywords: fine needle aspiration; pulmonary papillary adenocarcinoma; papillary thyroid carcinoma.

N Z J Med Lab Sci 2018; 72: 107-110

INTRODUCTION

Adenocarcinoma is the most common subtype of lung cancer (1,2). Pulmonary adenocarcinoma are histologically heterogeneous, presenting a wide range of histologic features including solid growth with mucin production, acinar, papillary, lepidic, enteric within the current WHO adenocarcinoma classification (2-10). Pulmonary papillary adenocarcinoma is a rare variant accounting for 7-12 % (2). This subtype of invasive non-mucinous adenocarcinoma is composed of true papillary structures in greater than three quarters of the tumour on histopathologic examination (2,3,11).

In this case report, we describe the classical morphologic features of a pulmonary papillary adenocarcinoma which resemble those of papillary thyroid carcinoma and discuss the utility of immunohistochemical staining in distinguishing primary from metastatic tumours.

CASE REPORT

A 63 year old male presented with a triangular shaped mass within the medial left upper lobe of the lung. On CT imaging the lesion measured 65 mm in maximum dimension. Additionally, there were numerous rounded, solid and ground glass nodules within the left upper lobe and right lung. There was no cavitation, hilar or mediastinal lymphadenopathy or background changes of chronic lung disease. Imaging features suggested the possibility of a primary lung malignancy, organising pneumonia, granulomatosis with polyangiitis, sarcoidosis or lymphoma. A CT guided fine needle aspiration (FNA) and subsequent core biopsy of the left lung mass were performed.

MATERIALS AND METHODS

The FNA sample was collected in SurePath preservative (BD Diagnostics TriPath, Burlington, NC) for liquid-based thin-layer preparation. The aspirate sample was spun at 600 rcf for 5 minutes. From the sediment, a SurePath slide was prepared and stained (Papanicolaou stain) using the SurePath prepstain machine. The remainder of the sediment was used to make a cell block, fixed in 10% formalin, embedded in paraffin, routinely processed and stained with Hematoxylin-Eosin (H & E). Immunohistochemical staining were carried out on the cell block and core biopsy sections using antibodies to thyroid transcriptor factor-1 (TTF-1), Napsin-A, Thyroglobulin, CD10, PAX 8, AMACR, CA19-9 and CD57 (Automated Ventana Bench Mark machine, the EnVision^{Tm} System).

RESULTS

Cytologic findings

SurePath and cell block preparations showed numerous fragments from a complex papillary neoplasm demonstrating true fibrovascular cores (Figures 1a 2a). The lining epithelial cells demonstrated prominent nuclear pseudo-inclusions and focal nuclear clefts and grooves (Figure 1b). The differential diagnosis therefore included metastatic papillary thyroid carcinoma, metastatic papillary renal cell carcinoma or primary pulmonary adenocarcinoma with a predominant papillary architecture.

Histologic findings

H & E stained sections of the lung core biopsy showed multiple fragments of a tumour having a complex papillary architecture. The papillae were lined by cuboidal cells with oval nuclei and prominent nuclear pseudo-inclusions (Figure 3a). There were suggestions of cilia on the luminal edge of the epithelial component and admixed lymphocytes. Based on these features and diffuse positive immunostaining for TTF-1 and Napsin A, and negative staining for Thyroglobulin, a diagnosis of primary pulmonary papillary adenocarcinoma was confirmed.

Immunohistochemical findings

Immunohistochemical staining on the cell block showed the tumour cells to be positive for TTF-1 (Figure 2b), Napsin A (Figure 2c) and negative for Thyroglobulin, CD10, PAX8, AMACR, CA19-9 and CD57 (Figure 2d). Immunohistochemical staining on the lung biopsy showed the tumour cells were diffusely positive for TTF-1 (Figure 3b) and Napsin A (Figure 3c), and negative for Thyroglobulin (Figure 3d).

PD-L1 immunohistochemistry was performed on formalin-fixed paraffin-embeded biopsy sections using the Roche clone SP263 (Ventana Optiview DAB detection system). PD-L1 staining by this methodology was negative.

Molecular analysis

EGFR testing was performed by IGENZ, Auckland using Mass Array Multiplex allele-specific PCR analysis (Agena Bioscience). EGFR testing on cell block sections showed no evidence of an activating mutation in EGFR, BRAF or KRAS genes.

Fluorescence in situ hybridisation (FISH) analysis was performed on biopsy sections using ZytoLight SPEC ROS1 and Vysis LSI ALK probe. This showed no evidence of an ALK (2p23) or a ROS1 gene rearrangement. However, loss of one copy of ROS1 was observed in 72 cells out of 100 cells examined.

DISCUSSION

Papillary carcinoma of the lung is an uncommon form of invasive adenocarcinoma accounting for 7-12% of the lung adenocarcinoma (2). In this subtype papillary structures normally replace the underlying alveolar spaces with complex branching papillae having true fibrovascular cores, lined by single or multiple layers of cuboidal to columnar glandular cells. The tumour cells exhibit moderate nuclear polymorphism, hyperchromatic nuclei and prominent nucleoli. The immunophenotype is similar to usual type pulmonary adenocarcinoma with positive immunostaining for TTF-1, Napsin A and Surfactant Apoprotein A (SPA) (1-5,8).

In a 1997 study papillary adenocarcinoma was classified based on histologic features by Silver and Askin (11). These tumours are composed of >75% papillary growth pattern. The behaviour of primary papillary adenocarcinoma is believed by some investigators to represent a more aggressive disease (1,7), while others have shown a similar 5-year survival between usual type adenocarcinoma [68%] and papillary-predominat adenocarcinoma [71 % 5-year survival]. Micropapillary tumours, as discussed below, are a more aggressive tumour subtype [38% 5-year survival] (12).

The true papillary adenocarcinoma of the lung needs to be distinguished from primary and metastatic micropapillary adenocarcinoma of the other organ including breast, urinary bladder, ovary and salivary glands (2,3,6,8,13). Lung adenocarcinoma with a micropapillary pattern were first reported by Silver and Askin in 1997 (11), then by Amin et al in 2002 (14). This tumour is characterized by small papillary tufts of neoplastic cells without fibrovascular core seen, mostly as detached clusters from the surrounding tumour in comparison to the well -defined true papillae in pulmonary papillary carcinoma (6-8,10,11,14).

Where available, a clinical history of a known extrapulmonary primary, along with the imaging findings and distinctive morphologic features are helpful in identifying a metastatic tumour in this site. Commonly primary lung carcinoma presents as a single nodule while metastases often present as multiple and bilateral nodules. However, as seen in this case, primary lung carcinoma may have intrapulmonary metastasis presenting as multiple nodules and so mimic extrapulmonary metastatic disease. In challenging cases ancillary immunohistochemical studies will be invaluable in defining a likely primary site.

Papillary adenocarcinoma resembling papillary thyroid carcinoma has been described in the lung, breast, kidney, prostate and pancreas (1,13,15,16). The combination of the classic nuclear features includes nuclear pseudo-inclusions, nuclear grooves, ground glass nuclei along with true papillary architecture that are considered standard diagnostic criteria for papillary thyroid carcinoma. A definitive distinction between a primary and metastatic tumour may be difficult on cytomorphology alone.

Positive immunostaining for TTF-1 and Napsin A, and negative staining for Thyroglobulin and PAX8 helped in the differential diagnosis and confirmed the lung primary origin of the tumour. Positive markers for lung primary and negative staining for CD10, PAX8, CA19.9, CD57 and AMACR excluded the renal, pancreas and prostate primary respectively.

Intranuclear pseudoinclusions as a single diagnostic pointer to the likely primary site of origin can be misleading as, in addition to their occurrence in papillary thyroid carcinoma, they are also evident in pulmonary papillary adenocarcinoma, hepatocellular carcinoma, melanoma, meningioma and variants of parenchymal renal cell carcinoma (1,13).

The frequency of EGFR, K-RAS and BRAF mutations varies in different subtypes of pulmonary adenocarcinoma. EGFR mutations are reported to be higher in papillary and micropapillary adenocarcinoma of the lung compared to other variants (7,8). Tumours with EGFR mutation may be more responsive to molecular targeted medicines such as tyrosine kinase inhibitors. Tumours with ALK and ROS1 gene rearrangements are responsive to crizotinib. Tumours with negative EGFR, ALK and ROS1 mutations are further tested for PD-L1. If PD-L1 is positive, pembrolizumab (Keytruda) may be used as first line immunotherapy (17).

In summary, the morphologic characteristics in the present case strongly resemble a papillary thyroid carcinoma. Definitive diagnosis of primary versus metastatic tumour was difficult without immunohistochemical studies. Awareness of the existence of papillary thyroid carcinoma like pulmonary adenocarcinoma will avoid misdiagnosis or unnecessary clinical and radiological investigations.

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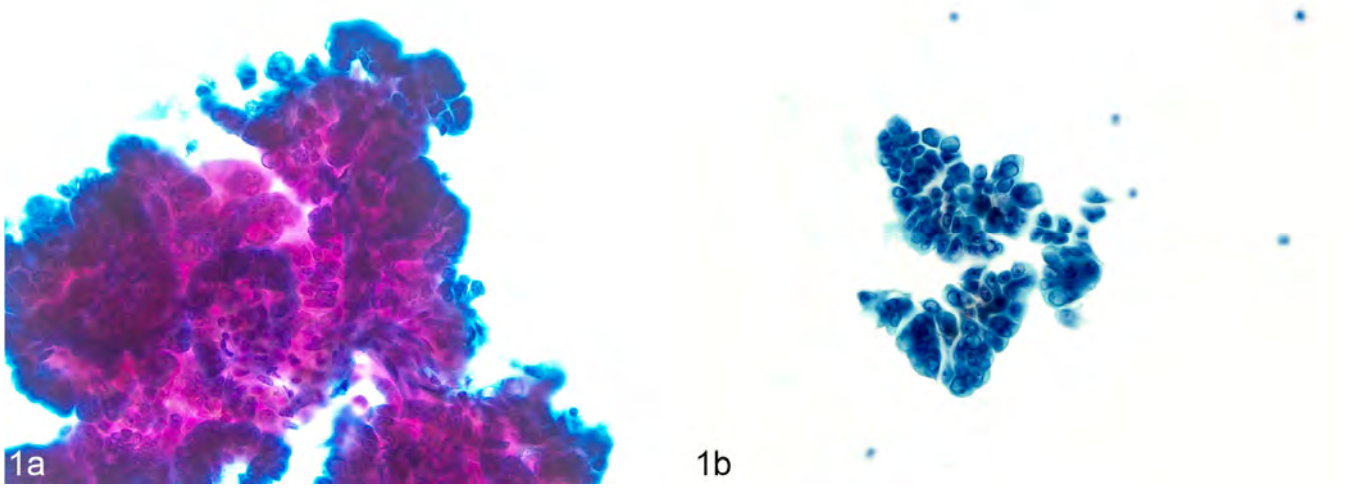

Figure 1a. Surepath preparations from FNA showing numerous complex papillary fragments demonstrating true fibrovascular cores. (Papanicolaou stain X 400).
Figure 1b. Showing tumour cells with prominent nuclear pseudo-inclusions and occasional nuclear grooves (Papanicolaou stain X 400).

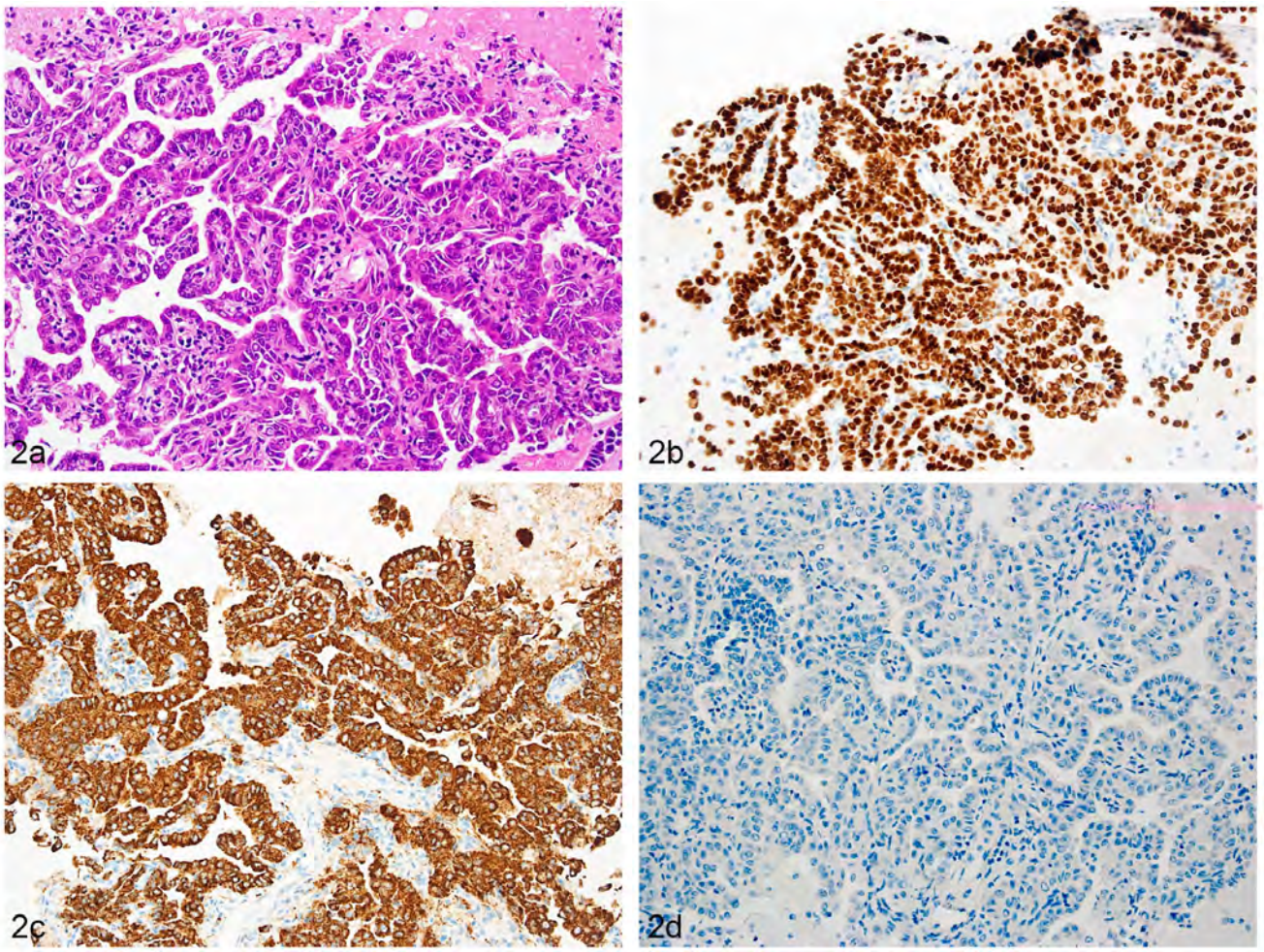

Figure 2a. Cell block from FNA showing numerous complex papillary fragments demonstrating true fibrovascular cores (H & E stain X 200).
Figure 2b. Immunohistochemical stain on cell block showing diffuse nuclear positive staining for TTF-1 (TTF-1 stain X 200).
Figure 2c. Immunohistochemical stain on cell block showing cytoplasmic positive staining for Napsin-A (Napsin A X 200).
Figure 2d. Immunohistochemical stain on cell block showing negative staining for Thyroglobulin (Thyroglobulin stain X 200).

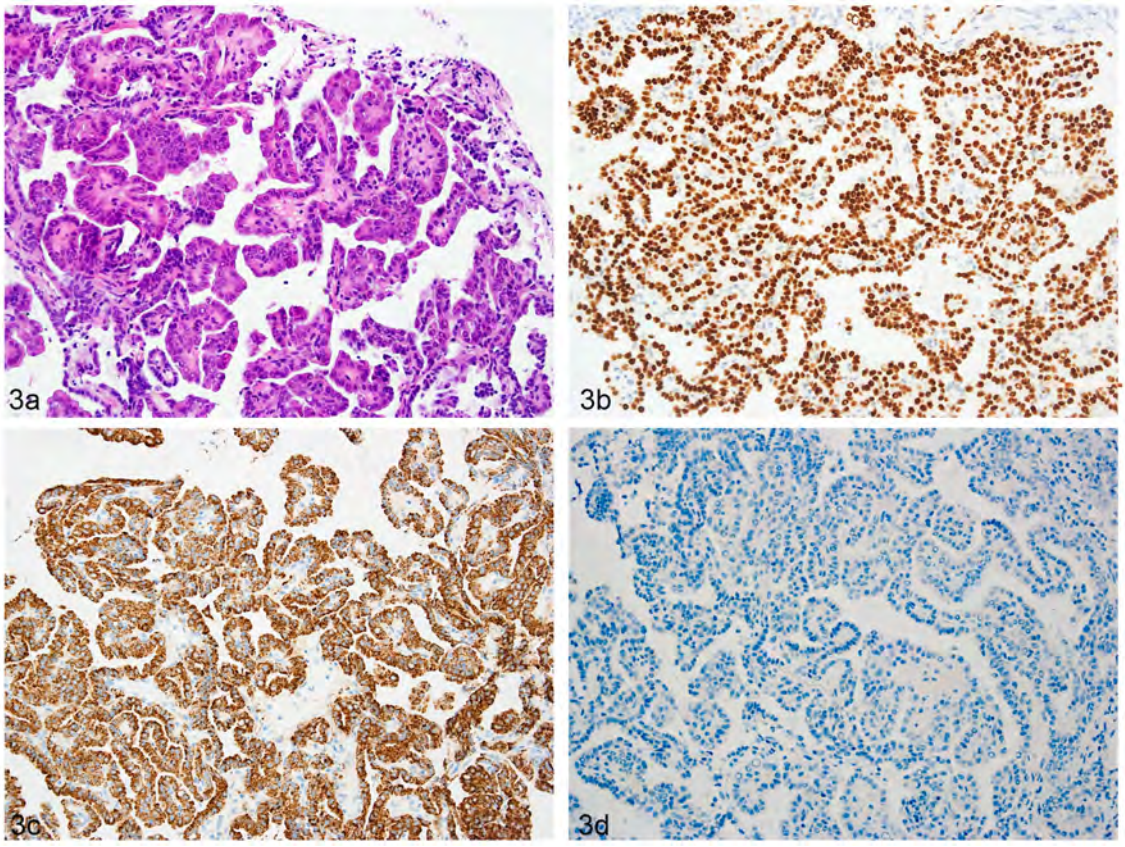

Figure 3a. Lung core biopsy showing complex papillary fragments demonstrating true fibrovascular cores predominantly (H & E stain X 200)
Figure 3b. Immunohistochemical stain on core biopsy showing diffuse nuclear positive staining for TTF-1 (TTF-1 stain X 200).
Figure 3c. Immunohistochemical stain on core biopsy showing cytoplasmic positive staining for Napsin-A (Napsin A X 200).
Figure 3d. Immunohistochemical stain on core biopsy showing negative staining for Thyroglobulin (Thyroglobulin stain X 200).

REFERENCES

1. Zhu YZ, Li WP, Wang ZY, Yang HF, He QL, Zhu HG, et al. Primary pulmonaryadenocarcinoma mimicking papillary thyroid carcinoma. *J Cardiothorac Surg* 2013; 8: 131.
2. Karmakar S, Nath A, Neyaz Z, Agarwal V, Ahsan S. Primary papillary adenocarcinoma of the lung: Report of two cases. *Lung India* 2017; 34 (3): 299-302.
3. Moran CA, Jagirdar J, Suster S. Papillary lung carcinoma with prominent “morular” component. *Am J Clin Pathol* 2004; 122: 106-109.
4. Zhang L, Johnston A, Shlyakhova N, Lin F, DeMay RM, Lu D. Metachronous adenocarcinoma of lung mimicking metastatic papillary thyroid carcinoma: A case report. *J Case Rep Images Pathol* 2015;1:17-21
5. Maeda R, Isowa N, Onuma H, Miura H. Pulmonary intestinal-type adenocarcinoma. *Interact Cardiovasc Thorac Surg* 2008, 7: 349-351.
6. Rudomina DE, Lin O, Moreira AL. Cytologic diagnosis of pulmonary adenocarcinoma with micropapillary pattern: does it correlate with the histologic findings. *Diagn Cytopathol* 2009; 37: 333-339.
7. Kerr KM: Pulmonary adenocarcinomas: classification and reporting. *Histopathology* 2009; 54: 12-27.
8. Cao Y, Zhu LZ, Jiang MJ, Yuan Y. Clinical impacts of a micropapillary pattern in lung adenocarcioma: a review *Onco Targets Ther* 2016; 9 : 149-158.
9. Rodriguez Dacic S, Pantanowitz L, Khalbuss WE, Monaco SE. Cytopathology of pulmonary adenocarcinoma EF, with a single histological pattern using the proposed International Association for the study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification. *Cancer Cytopathol* 2015; 123: 306-317.
10. De Oliveira Duarte Achcar R, Nikiforova MN, Yousem SA. Micropapillary lung adenocarcinoma : EGFR, K-ras, and BRAF mutation profile. *Am J Clin Pathol* 2009; 131: 694-700.
11. Silver SA, Askin FB. True papillary carcinoma of the lung: a distinct clinicopathologic entity. *Am J Surg Pathol* 1997; 21: 43-51.
12. Russell PA, Wainer Z, Wright GM, Daniels M, Conron M, Williams RA. Does lung adenocarcinoma subtype predict patient survival? A clinicopathologic study based on the New International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. *J Thorac Oncol* 2011; 9: 1496-1504.
13. Gritsman AY, Popok SM, Ro JY, Dekmezian RH, Weber RS. Renal-cell carcinoma with intranuclear inclusions metastatic to thyroid: A diagnostic problem in aspiration cytology. *Diagn Cytopathol* 1988; 4: 125-129.
14. Amin MB, Tamboli P, Merchant SH, Ordóněz NG, Ro J, Ayala AG, et al. Micropapillary components in lung adenocarcinoma: a distinctive histologic feature with possible prognostic significance. *Am J Surg Pathol* 2002; 26: 358-364.
15. Pailoor K, Kini H, Rau AR, Kumar Y. Cytological diagnosis of a rare case of solid pseudopapillary neoplasm of the pancreas. *J Cytol* 2010; 27(1): 32-34.
16. Naran S, Simpson S, Gupta RK. Cytologic diagnosis of papillary carcinoma of the breast in needle aspirates. *Diagn Cytopathol* 1988; 4: 33-37.
17. Troncone G. All-in-one: the dream and reality of molecular cytopathology testing on routine lung cancer smears. *Cancer Cytopathol* 2018; 126: 158-157.

BOOK REVIEW

Pacific Paramedical Training Centre. The First 30 Years, 1980-2010.

Author: Ron Mackenzie, QSO PhD FNZIMLS
Publisher: Ngia Press, Martinborough, New Zealand

The Pacific Paramedical Training Centre (PPTC) was established by Dr Ron Mackenzie and Associate Professor Sandy Ford at Wellington Hospital in 1980. Its main aim was to provide training and support for medical laboratory technicians from South Pacific countries. The PPTC had its genesis and practical beginnings at the Kew Hospital Laboratory, Invercargill where Ron was principal medical technologist. He set up short-term blood bank training modules there and provided logistic support to a number of South Pacific medical laboratories. Upon his move to Wellington as administrative technologist, Ron, together with Sandy Ford, continued these short-term courses and had discussions with the World Health Organization (WHO), New Zealand Red Cross and the New Zealand Ministry of Foreign Affairs, which ultimately resulted in the formation of the PPTC with their support.

The PPTC has been in operation continuously since 1980 and this book covers the first 30 years in a chronological order. The author has meticulously detailed all the courses held by the PPTC as well as other support measures, such as the establishment of the Pacific Regional External Quality Assurance Programme, recognition by WHO as a collaborating centre for external quality assessment in health laboratory services in 1990, a three year medical laboratory training course in Samoa, and distance learning programmes through the Pacific Open Learning Health Net.

A feature of this book is the many photos of Pacific Island laboratory technicians, together with teaching staff, who attended the many PPTC in-house short courses. Every single technician who attended one of these courses over the 30 years is also listed in an appendix, as are the Committee Members who oversaw the activities of the PPTC.

Throughout the text is mention of the many New Zealand medical laboratory scientists who assisted the PPTC in areas such as teaching, provision of equipment and books and consultancies; and to the many agencies that supported the PPTC continuously over the years, such as the Ministry of Foreign Affairs through the NZAid Programme, NZ Red Cross, WHO, Wellington Hospital Laboratory Services, New Zealand Blood Transfusion Service, Norman Kirk Memorial Trust, University of Otago Wellington and the NZIMLS. Also in the text are named the medical laboratory scientists who ran the PPTC, namely Andrea Hall, Mike Lynch, Gilbert Rose, Christine Story, John Elliot and Philip Wakem.

The founding principles of the PPTC were that teaching and development programmes offered *'must be appropriate, affordable and sustainable for the health care setting in which they will be used'*, with an emphasis on specialized and practical training to ensure an immediate benefit for the trainees and impact the health status of Pacific Island and neighbouring communities. To date, these principles remain the guiding ones.

In the foreword to this book Lady Jocelyn Keith, Past National President of New Zealand Red Cross, calls the PPTC '"a remarkable organization" that "punches well above its weight" and "a remarkable story of Kiwi resourcefulness and commitment". Ron Mackenzie has certainly demonstrated that in this delightful history of the PPTC. Copies of this book can be ordered for $25 from the PPTC, PO Box 7013, Wellington 6242, or email pptc@pptc.org.nz

Reviewed by Rob Siebers, Editor, New Zealand Journal of Medical Laboratory Science and Board Member, PPTC.

Science Digest

Contributed by Michael Legge

ABO blood type and severe trauma

The ABO blood group system is established by complex carbohydrates on red cell surfaces and the vascular endothelium as well as other cells and tissues. In recent years, research has implicated ABO blood type as a risk factor for various diseases including cancer, myocardial infarction and venous thromboembolism with the latter being rare in individuals with blood group O. In addition, the association of ABO blood groups and the risk of bleeding has been reported in the past. In the present research from Japan the association between the difference of ABO blood group and the outcome of severe trauma was investigated by a retrospective observational study (1). From a total of 901 patients comprising of type O, 32%; type A, 32%; Type B, 23% and type AB, 15%; blood group O was associated with the highest mortality (28%) compared with 13% for all other ABO blood groups. Transfusion volumes did not affect the data. The researchers noted that previous research has indicated that blood group of patients have 25 to 30% lower plasma von Willebrand factor (VWF) compared with those with other ABO blood groups which would increase the risk of haemorrhage. Previous research has shown that the highest levels of factor VIII and VWF were identified in: $A_1A/A_1B/BB$ genotypes with intermediate levels in: A_1/O and BO genotypes with the least in O/O genotype.

Antibiotic resistant typhoid in Pakistan

Spread through contaminated water up to 22 million cases of *Salmonella typhi* occur each year. If left untreated, typhoid fever can lead to intestinal haemorrhage and perforation of the bowel killing up to 15% of infected individuals, and estimates are that 200,000 people die each year. During the last six months over 2000 people have been infected with the XDR *S. typhi* strain (2). According to the National Health Institute in Islamabad the only oral antibiotic effective for the XDR strain is azithromycin. Alternatively, intra-venous antibiotics may be effective but are too expensive in low income communities. Vaccination programmes are underway but the situation is expected to get worse before any improvement. It is believed that the XDR strain emerged from *S. typhi* due to multiple antibiotic use and the possible plasmid transfer from *E. coli* with a drug resistance gene(s). International travelers from Pakistan have returned with XDR strain infections.

A novel approach to microbiology

Recent research from the USA has developed a novel microbial identification system based on biochip technology (4). The researchers developed a fully integrated, miniaturized semi-conductor biochip with closed tube chemistry detection system. The biochip was capable of performing multiplex amplification and sequence analysis with the capacity to perform comprehensive mutation analysis on up to 1000 sequences or strands simultaneously in less than two hours. In trials comparing conventional techniques with the biochip, the biochip correctly identified multiple DNA and RNA respiratory viruses using clinical samples as well as 54 drug resistance-associated mutations in six genes of *Mycobacterium tuberculosis,* all of which were correctly identified by next generation sequencing. The chip (8x8mm) is mounted on a circuit board (2x8cm) with fluidic ports and the data analysed using application software via a USB port.

Review of human papilloma virus (HPV) vaccination in males

Although human papilloma virus (HPV) infections are largely asymptomatic with the virus being cleared in the majority of cases, it still remains the most commonly sexually transmitted microorganism. Overall, approximately 10% of HPV infections persist and about 3% result in epithelial dysplasia and 1% result in cancer. Currently there are more that 200 different HPV types and these have been classified as high and low risk viruses. Of these there are two HPV types classified as high-risk cancer causing with HPV 16 and 18 the most common. In women about 100% of cervical cancers are attributable to high risk HPV types and in men approximately one third of penile cancers and 90% of oral cancers are attributable to high risk HPV types. Currently, a number of HPV vaccines are available: the bivalent against HPV 16 and 18; the quadrivalent against HPV 6,11,16 and 18, and a non-avalent which adds protection against a further five high risk HPV types. Whilst most industrialised countries have introduced female HPV vaccination, only five countries, including Australia, have introduced male HPV vaccination. In the review from Belgium, researchers identified 5196 articles, seven randomised control trials and three non-randomised studies and assessed them for efficacy, effectiveness and safety of HPV vaccinations in males of any age (3). Vaccine efficacy against permitting existing anogenital HPV infections was 49.9% and 88% for persisting oral HPV16 infections. Patients that were seronegative and PCR-negative had the highest degree of HPV vaccine induced protection from which the authors concluded that the use of the vaccines was most effective in HPV-naïve males prior to sexual activity.

Platelet counts during pregnancy

In uncomplicated pregnancies platelet counts of less than $150x10^3/mm^3$ are considered to be gestational thrombocytopaemia. This occurs in about 5 to 10% of women at the time of delivery with a general acceptance that it initially starts around mid-second to third trimester. Complications of pregnancy such as pre-eclampsia may also be associated with thrombocytopaenia. Recent research has investigated platelet counts in uncomplicated pregnancies over a four-year period in women aged between 15 and 44 years over the period of their pregnancies and up to 12 weeks post-partum (5). A total of 7,351 women had sufficient data for analysis and of these 4,568 had uncomplicated pregnancies and 2,586 had pregnancy related complications. Those with pre-existing thrombocytopaenia disorders totaled 197. In the uncomplicated pregnancies, the mean platelet count was $250x10^3/mm^3$ in the first trimester, $230x10^3/mm^3$ in the second and $217x10^3/mm^3$ in the third. At mean post-partum time of 7.1 weeks, a mean platelet count of $264x10^3/mm^3$ was found. Although a similar trend was observed in the pregnancy related complications, the platelet counts were significantly lower. The authors concluded that all pregnancies had gestation related platelet decreases, which, with the exception of the pre-existing thrombocytopaenia conditions, return to normal non-pregnancy levels post-partum.

A possible portable breast cancer diagnostic chip

According to the American Cancer Society about 40,290 deaths will occur this year due to breast cancer and in New Zealand about 600 deaths per year. Researchers in the USA have developed a microelectromechanical system (MEMS) biochip capable of measuring the mechanical properties of normal and tumour tissues (6). As a tumour progresses the mechanical properties (stiffness or elasticity) of the tumour changes that can be directly related to cancer progression. These changes are due to modification of the extracellular matrix associated with cancer cells. The researchers developed a biochip (10mm diameter) held in a 3D printer holder. Using paraffin blocks of normal and previously classified tumours from breast tissue 2mm plug of tissue was removed de-parffinized and then placed on the biochip sensor and the electrical conductivity over a programmed temperature range was measured. There was a statistically significant difference between normal and breast cancer tissues and it was proposed that this could be a diagnostic biomarker by using electro-thermo-mechanical properties of tissues.

Early detection of gestational diabetes

Gestational diabetes is associated with pregnancy complications for the mother, the fetus and the newborn. In addition, a longer-term outcome is the development of type 2-diabetes and cardiovascular disease in the women identified with previous gestational diabetes. Associated with maternal gestational diabetes is the risk of macrosomia and obesity in the children from such pregnancies. Although it can be diagnosed later in pregnancy there is increasing evidence that fetal overgrowth starts early rather than later during the pregnancy before the onset of gestational diabetes. HBA1c is used to screen high-risk pregnancies but not often used to identify any potentially at-risk, but otherwise apparently normal pregnancies. In recent research from the USA HbA1c was measured across all pregnancies from early pregnancy to term (7). Women in the 8-13 week gestation group (the earliest group) who had elevated HbA1c at that stage had a 22% increased risk of developing gestational diabetes. The researchers concluded that early HbA1c was more predictive the area under the curve (AUC) and that impaired glucose homeostasis was evident as early as 8-13 weeks gestation as indicated by HbA1c alone.

ZIKV in human semen

While ZIKV is transmitted primarily by mosquito bites, there are reports of the disease appearing in non-endemic countries and male-to-female transmission has been reported. In addition, the sexual transmission has been reported to enhance viral dissemination in the female genital tract and transmission to the fetus where ZIKV is known to be teratogenic. Further reports have indicated varying infectious viral load in human semen and it has been proposed that ZIKV may have an affinity for the male genital tract. Research, using animal models for ZIKV infections appear not to simulate the human male genital tract infections. Recent research from France supports the shedding of high viral loads in the male genital tract and has used testicular organ culture techniques to identify potential target tissue areas (8). The researchers identified that macrophages were the most susceptible cells in the testes to ZIKV infections, but the virus also infects and replicates in a wide range of testes somatic and germ cell lines. Semen collected from ZIKV infected men demonstrated an association of ZIKV with spermatozoa, however, the infection had no obvious deleterious effects on morphology and hormone production in culture. There was no significant inflammatory response identified in ZIKV infected men, which the researchers considered that it was the basis for persistent infection and warned for both horizontal and vertical transmission of ZIKV through infected testicular germ lines.

Significance of low serum bicarbonate

After haemoglobin,, plasma bicarbonate is the second most significant buffering system in the blood with minor buffering being provided by phosphate and protein. Generally, serum bicarbonate is associated with acid-base balance and is an important analyte in assessing acid –base balance. Two publications have identified an association with low serum bicarbonate and disease processes independent of acid-base status. The first from the USA using data for 2,287 individuals aged between 70-79 years who were part of a 10 year “Health, Aging and Body Composition Study” (9). The participants were grouped into three serum bicarbonate categories, <23.0 mEq/L; reference group 23.0-27.9mEq/L and high >28.0mEq/L. In the otherwise healthy participants with low serum bicarbonate but normal pH there was a 24% higher mortality risk regardless whether there was metabolic acidosis or respiratory alkalosis. Those with high serum bicarbonate showed no increase in mortality. The second publication from China is a study of 5318 participants aged between 18-70 years in a six-year observational research programme (10). The researchers identified that low serum bicarbonate over a two year follow-up period was associated with a 4% increases risk of developing an impaired fasting glucose, which would lead to insulin resistance and was independent of other risk factors for diabetes. Both research groups considered that monitored bicarbonate therapy might be beneficial in treating low serum bicarbonate to reduce both mortality and morbidity.

References

1. Takayama W, Koguchi H, Sugimoto M, Murata K, Otomo Y. The impact of blood type O on mortality of severe trauma patients: a retrospective observational study. *Crit Care* 2018; 22(1): 100.
2. Klemn EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, et al. Emergence of an extensively drug-resistant *Salmonella enterica* serovar typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *MBio* 2018; 9 (1): pii: e00105-e00118.
3. Harder T, Whichmann O, Klug SJ, van der Sande MAB, Wiese-Posselt M. Efficacy, effectiveness and safety of vaccination against human papillomavirus in males: a systematic review. *BMC Med* 2018; 16(1): 110.
4. Hassibi A, Manickam A, Singh R, Bolouki S, Sinha R, Jirage KB, et al. Multiplexed identification, quantification and genotyping of infectious agents using a semiconductor biochip. *Nat Biotechnol* 2018; 36 (8): 738-745.
5. Reese JA, Peck JD, Deschamps DR, McIntosh JJ, Knudtson EJ, Terrell DR, et al. Platelet counts during pregnancy. *N Engl J Med* 2018; 379 (1): 32-42.
6. Pandya HJ, Park K, Chen W, Goodell LA, Foran DJ, Desai JP. Toward a portable cancer diagnostic tool using a disposable MEMS-based biochip. *IEEE Trans Biomed Eng* 2016; 63 (7) 1347-1353.
7. Hinkle SN, Tsai MY, Rawai S, Albert PS, Zhang C. HbA_{1c} measured in the first trimester of pregnancy and the association with gestational diabetes. *Sci Rep* 2018; 8(1): 12249.
8. Matusali G, Houzet L, Satie AP, Mahé D, Aubry F, Couderc T, et al. Zika virus infects human testicular tissues and germ cells. J Clin Invest 2018; pii: 121735.
9. Raphael KL, Murphy RA, Shlipak MG, Satterfield S, Huston AK, Sebastian A, et al. Bicarbonate concentration, acid base status, and mortality in the Health, Aging and Body Composition Study. *Clin J Am Soc Nephrol* 2016; 11(2); 308-316.
10. Li S, Wang YY, Cui J, Chen DN, Li Y, Xin Z, et al. Are low levels of serum bicarbonate associated with risk of progressing to impaired fasting glucose/diabetes? A single-centre prospective cohort study in Beijing, China. *BMJ Open* 2018; 8(7): e019145.

THE Pacific WAY

New Zealand based training courses 2018, Pacific Paramedical Training Centre

Effective Laboratory Quality Management, 2nd July – 27th July.

The "Effective Laboratory Quality Management" course of 4 weeks duration was held at the PPTC between the 2nd and 27th July and four students attended : Aralai Tuione from Fiji, Ismael Barreto and Domingas Campos both from East Timor and Peter Tosul from Vanuatu.

Effective Laboratory Quality Management Class 2018

Haematology and Blood Cell Morphology, 6th August – 14th September

This course of six weeks duration was held at the PPTC between the 6th August and the 14th September and three students attended : Obwaia Buren from Kiribati, Julia Angelina from East Timor and Tonga Havili from Tonga.

Haematology Class 2018

Microbiology, 24th September – 19th October 2018

This course of four weeks duration course was held at the PPTC between the 24th Sept and the 19th October and seven students attended: John Kave from PNG, Meleage Tapuala from Samoa, Majory Kwaina and Anicia Havimei from the Solomons, Yasith Ros and Dariven Phann from Cambodia and Ishael Ken from the Marshalls.

Microbiology Student tour of Environmental Science and Research Porirua

The PPTC wishes to thank Audrey Tiong for presenting to the students an explanation of the processes surrounding culture collection and the significance of QC strains. AMR national antimicrobial surveillance was also discussed.

Microbiology Class 2018

Remaining PPTC courses for 2018

Blood Transfusion Science: 5th – 30th November 2018 (4 weeks). Lecturer: Susan Evans

This course will include units of study covering the theoretical and practical aspects of the following topics: routine blood grouping, blood group antigens, crossmatch techniques, antibody detection, transfusion reactions, haemolytic disease of the newborn, screening blood for infectious agents, blood donor selection, organisation of a blood bank and the appropriate use of blood components in transfusion medicine.

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Pacific Islands Society of Pathologists

Phil Wakem, the PPTC's CEO was fortunate to be invited to participate in the Inaugural meeting for the Pacific Islands Society of Pathologists (PISP held in Suva, Fiji on the 27th – 28th September 2018. The meeting was jointly sponsored by the Secretariat of the Pacific Community (SPC and Fiji National University (FNU. The meeting consisted of presentations from participating Pacific Islands countries, External Agencies and group work.

Background

Globally the need for access to high quality health care is increasing. The increase in driven by social, economic and demographic factors and the Pacific region is no exception. The progress to high quality health care is not possible without the availability of a Pathologist service that ensures accurate and timely diagnosis of disease, leading to correct and effective treatment and management of patients. Across the Pacific region there are major gaps in the availability of Pathologists and quality of health laboratory services that exist in each of the Pacific Island countries. The gaps exist in the areas of effective advocacy, infrastructure, laboratory quality assurance, testing standards, education and training and workforce development. The main purpose of the Pacific Islands Society of Pathologists is to address these gaps with the objective to strengthen its member service and overall quality of Health Laboratory Services in the Pacific.

Meeting Objectives

The established objectives for the meeting can be described as follows:

- Confirm establishment and membership of the Pacific Islands Society of Pathologists (PISP)
- Collate data on pathologist/laboratory situations in the region (situational analysis)
- Identify further needs to be included in the "Postgraduate" training program offered by the Fiji National University
- Revisit external organization assistance to specialist training in pathology and strengthening of health laboratories across the Pacific
- Formulate plans for continuous medical education/ professional development and proficiency testing for pathologists

Phil was invited to give a 15-minute presentation on how the PPTC has been assisting the development of Pathologists and the strengthening of laboratories in the Pacific and the further PPTC assistance that may be able to be offered to the Pacific Islands Society of Pathologists in the future.

Quality improvement of laboratory services for viral hepatitis in the Western Pacific Region

A WHO initiated meeting was conducted in Manila (Philippines) on the 26th -27th June, the objective of which was to discuss current status and issues involving viral hepatitis laboratory services in the Western Pacific Region with the development of recommendations for improving quality of laboratory services in Pacific countries. This meeting was also responsible for "terms of reference" development of the regional viral hepatitis laboratory network including roles and responsibilities of Regional/National Reference Labs. Blood safety was also addressed.

The PPTC was invited as an advisor to present on its External Quality Assurance Program and the laboratory support it provides to resource limited countries.

Navin Karan, the PPTC's Programme Manager and Microbiology expert represented the PPTC at this meeting and contributed to the presentation of specific aspects of EQA in the Pacific:

- Challenges of EQA on HIV, viral hepatitis and STIs in countries
- Needs and concepts of a viral hepatitis regional laboratory network
- The support of EQA in and by countries

Pacific Islands Society of Pathologists Meeting 2018

- The strengthening of EQA systems as partners
- Feedback, recommendations on improvement actions on laboratories which have outliers
- The cost-effectiveness of EQAS models for viral hepatitis sustainability

Training workshop to strengthen influenza-like illness (ILI) and severe acute respiratory infections (SARI) surveillance

As part of the CDC support in strengthening Influenza testing and surveillance in the Pacific, the Secretariat of Pacific Countries invited the PPTC to attend a one week training workshop on ILI and SARI surveillance in Suva, Fiji from 6th - 10th August 2018. The established objectives for this training were:

- To discuss the state of laboratory capacity for human health and influenza disease surveillance in the Pacific
- To discuss ways to better maintain the operation of ILI and SARI surveillance in the Pacific
- To identify the gaps, challenges and opportunities for strengthening ILI surveillance in human
- To consider potential research opportunities in 2 settings: in human health in the context of laboratory and surveillance
- To provide influenza vaccine updates and opportunities

Informal Consultation on the Quality Improvement of Laboratory Services for Viral Hepatitis in the Western Pacific Region
26-27 June 2018, Manila, Philippines

Navin Karan represented the PPTC at this meeting and presented to those in attendance the use of the Gene Expert in Pacific Island laboratories as well as a comprehensive overview of laboratory quality management Systems.

Journal Questionnaire

Below are ten questions based on articles and the Science Digest column from the November 2018 issue. Read the articles carefully as most questions require more than one answer. Answers are to be submitted through the NZIMLS website. Make sure you supply your correct email address and membership number. It is recommended that you write your answers in a word document and then cut and paste your answers on the web site.

The site has been developed for use with Microsoft's Internet Explorer web browser. If you are having problems submitting your questionnaire and you are using the Firefox web browser, try re-submitting using Microsoft's Internet Explorer.

You are reminded that to claim valid CPD points for successfully completing the journal questionnaire you must submit an individual entry. It must not be part of a consultative or group process. In addition, members who have successfully completed the journal questionnaire cannot then claim additional CPD points for reading the articles from which the questions were derived.

The site will remain open until Friday 15th March 2019. You must get a minimum of eight questions right to obtain five CPD points. The Editor sets the questions but the CPD Co-ordinator, Jillian Broadbent, marks the answers. Direct any queries to her at cpd@nzimls.org.nz.

NOVEMBER 2018 JOURNAL QUESTIONNAIRE

1. Resistance to carbapenems can be caused by which mechanisms?
2. What are some of the epidemiological risk factors(s) for the acquisition of CPE?
3. What is the recommended screening carbapenem for the detection of CPE and what breakpoints should be used?
4. Name two phenotypic methods which would be suitable for confirmation of CPE.
5. When should the presence of CPE be notified to the clinical microbiologist and infection prevention services?
6. Name the range of histological features of pulmonary adenocarcinoma.
7. What are considered standard diagnostic criteria for papillary thyroid carcinoma?
8. Intranuclear pseudo inclusions are present in what other malignancies than papillary thyroid carcinoma?
9. Recent research has implicated ABO blood type as a risk factor for which diseases?
10. During tumour progression stiffness or elasticity of the tumour increases. What are these changes due to?

AUGUST 2018 JOURNAL QUESTIONNAIRE AND ANSWERS

1. Name possible aetiologies for biliary atresia.
   Infections such as cytomegalovirus, Reo virus III, Epstein-Bar virus, rubella virus, α-1-antitrypsin deficiency, Down syndrome, congenital atresia.
2. What are the usual causes of giant cell hepatitis?
   Various degrees of insult to the immature liver, can be idiopathic or caused by maternal viral hepatitis.
3. What are the two main functions of bile?
   Carrying of toxins and waste products out of the body and facilitating the emulsification and digestion of fats.
4. Basophilic stippling caused by denatured RNA fragments is associated with what?
   Heavy metal poisoning, haemoglobinopathies, severe infections, sideroblastic anaemia, megaloblastic anaemia.
5. Caesarean delivery is often indicated in mothers with immune thrombocytopenic purpura to prevent what?
   Risk of intracranial bleeding associated with vaginal delivery.
6. Preterm newborns are often associated with thrombocytopenia following what?
   Chronic hypoxia-induced suppression of megakeryopoiesis.
7. The emergence of multi-drug resistance patterns is due to the presence of which mobile genetic elements?**Plasmids, insertion sequences, integrons.**
8. What is the most common mechanism by which Gram-negative bacteria capture gene cassettes?
   Incorporation of resistance genes into resistance integrons.
9. What may contribute to the development of antibiotic resistance through selective pressure?
   Irrational use of antibiotics in the treatment of human and animal infections, and in animal food.
10. Integrons play a major role in spreading what?
    Antibiotic resistance genes which are present in Gram-negative bacteria.

The New Zealand Institute of Medical Laboratory Science (Inc)

Presents the

2018 Mortuary SIG Seminar

Wellington Hospital
830am to 5pm
REGISTRATION FEES
Members: $120
Non-Members: $175
Saturday Dinner: $60 pp

Nov
10

Presentations Invited. Contact Samantha Marshall
samantha.marshall@wellingtonscl.co.nz

Registration will be available at www.nzimls.org.nz

Immunology Special Interest Group 2018

Saturday 17 November 2018
Wellington Hospital, Education Lecture Theatre

Confirmed speakers:

Dr Richard Steele, Immunopathologist

Dr Tim Blackmore, Microbiologist

James Rice-Davies, HIV/ID Clinical Nurse Specialist

Louise Wienholt, Manager Business Development and Blood Disciplines, RCPAQAP

Dr Russell Barker, Immunopathologist

Presentations are encouraged from all specialities

Auto Immune
Infectious Diseases
Allergy

Contact Sarah Burge:

Sarah.burge@wellingtonscl.co.nz

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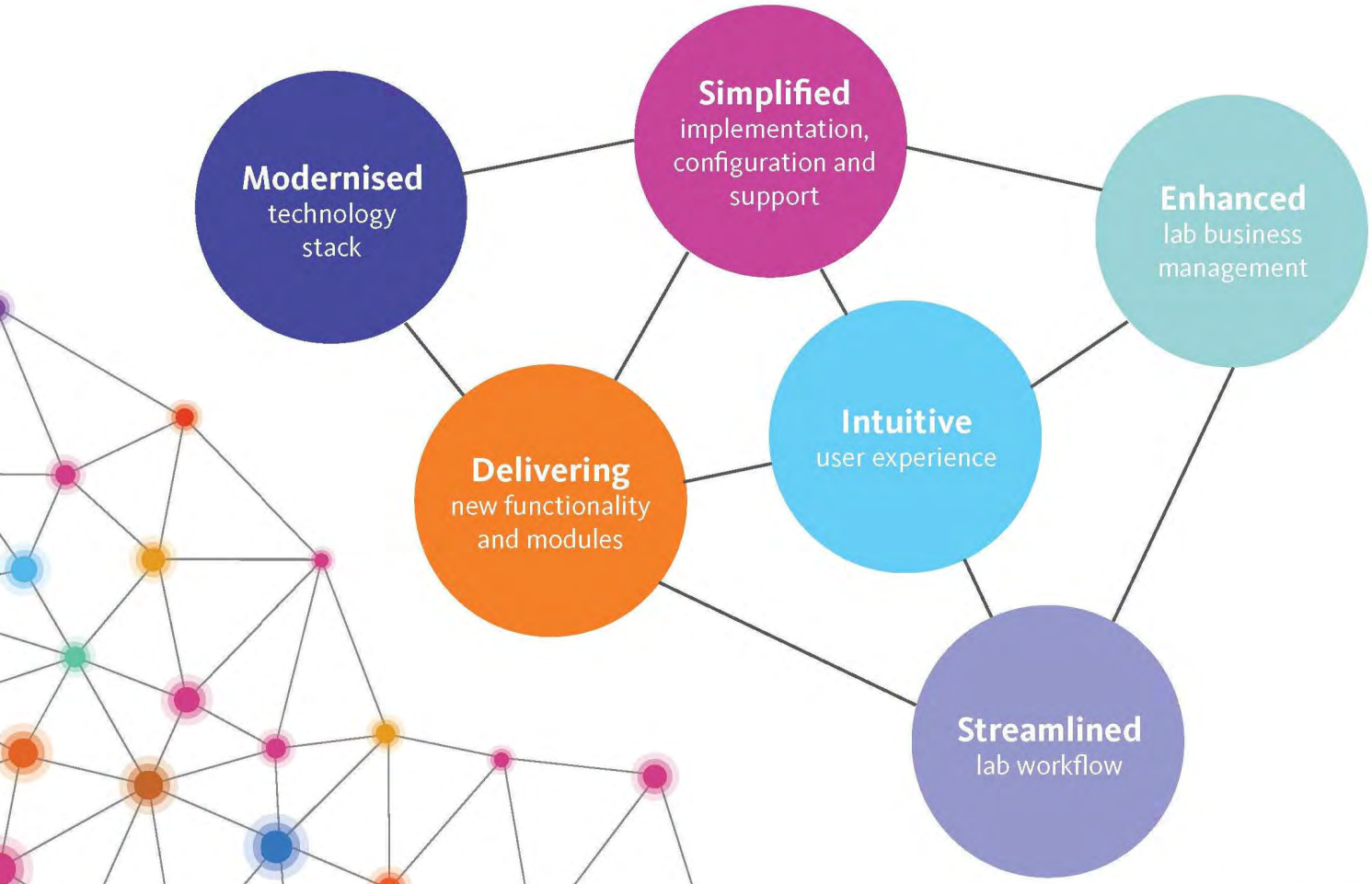

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