**Post Antibiotic Era Signs**

**Carbapenemase Resistant Enterobacteriaceae (CRE)**

ESBL and CRE are acronyms to help delineate antibiotic resistance which may be borne by species of the family Enterobacteriaceae which includes many species (e.g. E. coli, Klebsiella, Proteus, Salmonella, Shigella, etc) commonly found and often shared in the bowel flora of man and animals (e.g. E. coli).

These same species provide shared faecal flora to a certain/large extent directly between man and animals and so to the environment.

*Campylobacter* is not usually colonised in humans unless ill, does not belong to Enterobacteriaceae, but also in keeping with *E. coli* has a bowel source in animals/birds - and we ingest this bowel flora commonly not only between humans from touched surfaces (note rapid faecal-hand norovirus spread when present is a clear indicator of how much we routinely share our bowel flora – often 30-50% infection rate in an outbreak within 3 weeks) but also from any faecally contaminated bowel source via chicken meat, contaminated waterways, etc (cattle are actually the largest likely reservoir of campylobacter concentration in terms of campylobacter microbial numbers but less our food chain contamination in NZ). We ingest campylobacter in sufficient quantities (average person needs to ingest around 500 campylobacter to overcome our immunity, so actual ingestion rates are much higher but often only transiently colonised and not detected) to cause reported infection in NZ 7,000 times annually – but only around 1 in 7 to 10 people with gastro seek medical advice, so actual clinical infection incidence will be around 50-70,000 people per year in NZ (and transient, sub clinical colonisation by campylobacter and so *E. coli* also, will be much higher than this again).

That is a marker only of our shared animal faecal sharing, but because *E. coli* is more common in animals than campylobacter and has lower pathogenicity on ingestion, our actual ingestion rate of *E. coli* will be much higher still.

NZ uses over 60 tons of antibiotics for non medical use each year, so we know even when looking at known pathogens e.g. campylobacter as reported in recent NZ chicken common resistance to fluoroquinolones and tetracycline from 3 of 4 major suppliers tested, let alone commensal flora (e.g. *E. coli*) which has no or little routine surveillance of antimicrobial resistance in animals (or bowel flora of humans for that matter). These resistance plasmids are easily transferrable amongst species e.g. *E. coli*, and although Klebsiella is not such a common bowel flora species as *E. coli* is, Klebsiella has the ability to very rapidly pick up resistant plasmids when both it and the plasmids are present (e.g. in *E. coli*) and this becomes an extra issue where Klebsiella is found more commonly to cause infections e.g. the hospital environment

So, the bowel flora, environment and food chain of man/animals/edibles and the environment are somewhat of a continuum, commonly sharing and harbouring Enterobacteriaceae also.

This is unlike *Staph. aureus* (whether MSSA or MRSA), which is primarily skin borne and primarily not in the bowel or ingested to colonise in the bowel.

*Staph. aureus* is much less commonly found in the wider environment (excepting human touched surfaces, skin scales deposition and to a small degree companion animals, sometimes pigs, etc)

This routine bowel flora sharing helps explain why ESBL, and more latterly CRE, is spreading so fast worldwide compared to what MRSA has.

Faecally sourced organisms are shared more regularly than we would naturally be emotionally comfortable with. This sharing occurs routinely amongst other humans, animals, and so water borne and from there to the food chain - including vegetables/manure and shrimps, shellfish – the latter two often located, especially overseas, below sewage works as a source of food/manure for them which they in turn can concentrate.

So in addition to human to human sharing, all food and water sources are also efficient vectors of Enterobacteriaceae (including, perhaps especially *E. coli*, including associated ESBL and CRE when present).

**And this includes imported foods.** Food is endemically contaminated in endemic countries, and from there imported/exported around the world, with little or no surveillance. Carbapenem resistant *E. coli* is thus endemic in these endemic areas food, and ours as we import it or as we ingest it there as a visitor/traveller, or here.
20+ years ago shrimps from Chch delicatessens were tested at our food and water testing lab at the time of interest for microbial resistances – multiply resistant *E. coli* isolates were cultured including resistance to *gentamicin*. These were imported shrimps, and their farming process in Asia includes growing/harvesting shrimps in dug out water pits - when the shrimps show signs of stress/disease, antibiotics are added. When more stress/disease a different antibiotic is used until the cost benefit line is breached. New pits are then dug and the whole process repeated.

This food and water chain source should not be underestimated as an ESBL/CRE source for our own bowels, especially from overseas visitors, migrants, and NZers (including HCW’s) travelling to those countries that have CRE or ESBL endemically – this includes India, South Asia, the Mediterranean, Spain, the Balkans - and from there lower but increasing occurrences to those that travel there including USA, UK.

For instance

1. Kuenzli et al. BMC Infectious Diseases 2014, 14:528  
   http://www.biomedcentral.com/1471-2334/14/528

**Swiss study**

Between December 2012 and October 2013, healthy travellers who planned to travel to South Asia (India, Bhutan, Nepal and Sri Lanka) from German speaking Switzerland, were enrolled in the study. Clients travelling for more than five weeks, travelling to other countries than India, Bhutan, Nepal, and Sri Lanka or to more than one of these countries, were excluded from participation. Only 2.8% were ESBL positive on screening pre travel, but 69.4% post travel, 86.6% ESBL positive post travel to India. A particular risk factor was eating ice cream or pastry (Odds Ratio increased 3.90)

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<th>Table 4: Prospective studies on travel-associated colonization with ESBL-producing Enterobacteriaceae – rates and risk factors</th>
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<td><strong>Travellers (n) overall</strong></td>
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| Current study | 170 | 69.4 | 68 | 86.8 | Travel Destination  
Visiting Friends and Relatives  
Consumption of Ice Cream & Pastry |

*Risk factors for becoming colonized for all the countries included in the respective study.  
Risk factor for colonization with *E. coli* resistant to gentamicin, ciprofloxacin and/or third-generation cephalosporins  
South Asia (not specified).  
South Asia: Bangladesh, India, Maldives, Nepal and Sri Lanka.

“**Conclusions:** High colonization rates with ESBL-producing Enterobacteriaceae were found in travellers returning from South Asia. Though risk factors were identified, a more common source, i.e. environmental, appears to better explain the high colonization rates”

2. **CRE Acquisition by healthy visitors from France to India**

3 of 57 travellers colonised with CRE (yellow highlite), but also other resistances as well, below:

www.eurosurveillance.org 19 March 2014 / published on 10 April 2014
A positive of this study being that the colonisation of CRE was for less than 3 months in these healthy travellers.

Debilitation and antibiotic use increase colonisation times.

Food for Thought Questions:

1. Should staff (and patients) who have recently travelled to CRE endemic countries also be screened on return, and if a staff member was CRE positive/colonised what would we do or would we rather not know (probably)??
   CRE colonised staff would likely be a higher CRE cross colonisation/infection risk than a patient (more patient contact, average NZ DHB 20% non compliant hand hygiene rates)

2. Should equal extra vigilance for finding CRE colonisation be used for higher risk patients as well as higher risk food as possible CRE cross infection/colonisation sources?
   e.g. higher risk (imported) foods from CRE endemic countries as potential CRE sources? And what would/could we do if they were positive (legally, trade barriers, etc to consider)

3. If a CRE carrier is found in any longterm care situation, e.g. rest home, should or can they be isolated for the rest of their life and/or colonisation period if colonisation was to be lost? I do not think so

Testing requirements to consider

- Most studies show at least two negative rectal swabs are required to relatively reliably rule out CRE (and in addition to that different isolation media each have their own benefits and draw backs – cost and sensitivity)
- Should we test significantly wider and more – at least initially to see if any positives arise and where from. Then re evaluate frequency and sources, but consider annual repeat at least to better gauge any increase colonisation
- How much budget is available, how thorough/scientific do we wish to be, what changes would these testing results bring about?
Appended below some epidemiology. Note carbapenems only became available around 1980, and resistance first really noted only in early 1990’s. This is a dramatic and rapid spread rate of resistance in 20+ years compared to MRSA spread rate after 50+ years.

Spread of different forms of CRE:


And carbapenemase resistance in Acinetobacter species, usually more ICU associated infections:
“The rapid and global expansion of carbapenem-resistant Gram-negative bacteria (i.e. carbapenemase-producing Enterobacteriaceae and carbapenems-resistant A. baumannii) during the past decade is a worrisome trend and a threat to healthcare and patient safety in Europe and globally. The consequences for patients infected with these bacteria are fewer options for treatment, and increased morbidity and mortality. Given that there are few novel antimicrobial agents that are likely to become available for clinical use in the short to medium term, the risks to public health are not difficult to fathom.”

And spread for one only of the carbapenem groups (New Delhi metallo-beta lactamase 1):

http://eurosurveillance.org/ViewArticle.aspx?ArticleId=20809

Note India 52.3%
Routine **travellers** risk of becoming colonised with **ESBL** (same reservoir and transmission route as CRE):

Clinical Infectious Diseases Advance Access published January 21, 2015

http://cid.oxfordjournals.org/content/early/2015/01/07/cid.ciu957.full.pdf
“Conclusions: Travellers Diarrhoea (TD) and antimicrobials for TD proved to be independent risk factors, with up to 80% of TD+AB+ travellers contracting ESBL-PE. In modern pre-travel counselling for those visiting high-risk regions, travellers should be advised against taking antibiotics for mild or moderate TD.”

The world is becoming smaller – food production, travel, trade, immigration coupled with total antimicrobial use all have a part to play in emergent MDRO’s. Focussing on one component only by screening has some likely benefits, primarily perceived and/or educational awareness benefits, but we must be very aware it will only ever be a small part of a much larger picture. **Known MDRO positive carriers or patients are not the problem**, other than reduced treatment options to themselves, they are a symptom of a much larger issue.

**There will always be many more people (and foods) colonised with MDRO’s than we know are positive**, so there will likely be associated risks if/when staff place most of their Standard Precaution energies into known positive carriers/patients only, thus by definition, less precautions for others not known to be positive – this is a significant risk, and as we learnt from before the implementation of ‘Universal Blood Precautions’ in the 1970’s for hepatitis/HIV, a counterintuitively dangerous approach.