Conference Report: The Wound Infection Summit

Kings College Hospital, London; March 2013

*We report on the first **Wound Infection Summit**, which took place at Kings College Hospital, London, on 20th March 2013. This one day meeting was chaired by Professor Keith Cutting, and highlighted the latest scientific and clinical issues in wound infection.*

The aim of the Wound Infection Summit was to identify and assess new ways of reducing wound infection, from biofilm use, to exploring microbial content in devitalised tissue. The meeting was organized by UK Health Gateway (http://www.ukhealthgateway.com).

Looking at wounds from a fresh perspective

The first presentation was by *Professor Keith Cutting, visiting professor at Buckinghamshire New University* and was entitled: Wound infection criteria – where are we now?

He discussed the importance of consensus in wound infection criteria, using the EWMA position document 'Identifying criteria for wound infection' as an example. This was a review of criteria common to six wound types by a panel of 54 international multi-disciplinary healthcare professionals, using the Delphi process to identify criteria.

The panel found the following infection criteria specific to wound type:

- Acute wounds (primary and secondary): cellulitis, pus/abscess
- Diabetic foot ulcers (DFU): cellulitis, lymphangitis, phlegmon, purulent exudate, pus/abscess
- Arterial leg ulcers: cellulitis, pus/abscess
- Venous leg ulcers: cellulitis
- Burns: cellulitis, ecthyma gangrenosum – focal areas of discolouration
- Pressure ulcers (PU): cellulitis, crepitus, viable tissues turn sloughy.

Interestingly, all panel findings were consistent with the 1994 guidelines by Cutting and Harding on identifying wound infection (Cutting KF, Harding KG. Criteria for identifying wound infection. *J Wound Care* 1994;3:198–201) – therefore providing validation for these guidelines.

One aim of the EWMA study was to achieve consensus; Professor Cutting asked "when is it [consensus] achieved?", pointing out that a Cronback's Alpha score of greater than 70 indicates consensus, but that clinicians, however, appear to use their own set of criteria. He commented that there is no working consensus, and that this multidisciplinary panel was the first attempt at achieving consensus in six wound types.

Moving on to discuss biofilms, he made the point that diagnostic tools for biofilm diagnosis are limited. There is no diagnostic test for biofilms, but there are ways of analysing wounds which probably contain biofilm – discussing some picture examples, he pointed out that the wounds resisted all attempts at management and one in particular demonstrated a 'slimy' appearance – clues that they may be infected with biofilm. Scanning electron microscope pictures were reviewed – he pointed out again that these showed morphology consistent with *Streptococcus* infection, and some sort of slime – and that again this was suggestive of biofilm presence.

He highlighted the validity and benefit of looking at wounds with 'new eyes', quoting from Proust: "The real voyage of discovery consists not in seeking new landscapes, but in having new eyes". He made the point that if we practice and get used to this cryptic message, then we can decipher it with time. We need to learn to interpret what we see (and hear). He pointed out that we cannot generate guidelines that are case-specific – they have to be broad, and then they do not always apply to individual cases.

With that in mind, Professor Cutting returned to the Delphi criteria. He concluded that we need to validate the Delphi criteria and look at them by wound type – we therefore need to look at wounds with new eyes.

Novel methods are needed for assessment of device effectiveness

Grahame Wilkinson (London School of Economics) delivered a presentation entitled: The cost of wound infection.

Mr Wilkinson began by highlighting the following figures:

- Approximately 200,000 people (in the UK) have a chronic wound
- The prevalence of open leg ulcers in the UK is approximately 0.12–0.32%, and treatment is primarily through community nurses
- The cost to the NHS of caring for patients with wounds is 2.3–3.1 billion/year (estimated 2006)
- Wound dressing costs increased from £80 million in 2003 to £112 million in 2008 – the greatest increase in costs was due to use of silver dressings. A 40% increase in cost was seen, with a 15% increase in the number of items prescribed
- Cost in 2002 was £4 million (120,000 items); cost in 2008 was greater than £24 million (400,000 items), and recently costs haven't decreased or increased.

He commented that the NHS MeReC Bulletin on evidence-based prescribing of advanced wound dressings for chronic wounds in primary care (June 2010) states that "there is no robust evidence that dressings containing antimicrobials (e.g. silver, iodine or honey) are more effective than unmedicated dressings for the prevention or treatment of wound infection." He also commented that NICE Guideline CG74 states that there is no evidence even to support provision of specialist wound care services, and asked "do people developing guidelines engage with practitioners in the field when developing them?"

He pointed out that when people purchase medical devices they tend to want to buy the cheapest, and that dressings are grouped by what they're made of, not by what they do – asking "does benchmark pricing encourage investment and innovation?", while making the point that restricting medical devices by category does not take their actual clinical value, advantages and associated time-savings into account – this is restrictive for companies in terms of innovation.

NICE makes appraisals using quality of life years (QALYs) using the EQ5 D measure (this asks, does [the product] make you live longer and improve QoL?) The problem with using this system to assess wound dressings and devices is that small differences in QoL are not picked up. NICE has therefore developed the Medical Technologies Evaluation Program (MTEP) to select and evaluate new medical technologies – this has relaxed evidence requirements but requires that adoption of devices must not increase NHS spend.

Devices are therefore treated (and evaluated) differently from pharmaceuticals, and must be more effective and cheaper to be recommended by NICE. There are, however, key differences between devices and drugs. The skill of the practitioner (user effect) is also

important with devices. Further, indications are tightly specified with pharmaceuticals, while they are often looser with devices.

We need to develop new methods of assessing device effectiveness and capturing this in an economic model.

He made the point that clinical trials for devices are difficult to blind/randomize, and the benefits measured by QALYs are too narrow, using Oxford Hip Score mapping as an example – very specific evidence is captured, then mathematic and statistical methods are used to map this onto EQ5D – confidence, utility are developed to NICE standards.

Physician preferences carry a lot of influence on device selection – and these are being taken out of the equation as health services are trying to standardize to the cheapest options. The health service perception is that there is no evidence; you therefore have to create your own evidence. He pointed out that NICE do have funding for research projects – clinicians can lobby NICE for investment in research – but that industry hasn't developed the clinical trial base (due to not enough funding). He concluded that the evidence base just isn't there for devices, especially in relation to QALYs. The device industry is characterized by smaller companies, and can't really compete – he made the point that he could foresee a number of take-overs in the next few years, with a move towards larger companies which were capable of more investment into research study.

Dressings – an important factor in managing wound bioburden

Professor Richard White (University of Worcester) presented a talk entitled: Passive mechanisms for managing wound bioburden.

He began by saying that research has given those in wound care a changing perspective over the years – encouraging discussion and thought. Reviewing the point 'antibiotic resistance poses a catastrophic threat', he pointed out that he has heard this many times in the past 30 years, and that although drug discovery was posited by Sally Davies as one potential solution, ***antiseptics*** may be another.

Bioburden control may be active or passive.

Active bioburden control involves killing the bioburden and uses antimicrobials.

Passive bioburden control involves the following:

- Fluid handling – to what extent does the removal of planktonic organisms affect wound healing?
- Occlusion – this is less discussed, what are the effects? Occlusion is associated with a reduced incidence of infection and also provides a 'barrier' function
- Barrier function – keeps the wound from being exposed to body micro-organisms which are potentially infective
- Dead space – surgeons don't like closing wounds and leaving a visible void, as this is thought to be a potential micro-environment for bacteria. What impact does the dead space between the dressing and the wound bed have?
- Sequestration – removal of bioburden by passive methods
- Virulence determinants – how does this impact on the wound, the tissue and the individual?

Any adaptation by which organisms might improve their survival is based on basic evolutionary forces. Practitioners should regard the wound as an environment – and one that is good for bacteria to thrive in.

How can we disrupt that environment?

He discussed the points on passive mechanisms in infection control made by Lawrence (1994) – one of which was that dressings can minimize the airborne dispersal of potentially pathogenic micro-organisms (Lawrence 1994, Am J Surg 167:1A:21S-24S).

Fluid handling is also important in passive infection control; the practitioner should try to achieve an optimally moist wound environment, preventing wounds from becoming too wet as both *Pseudomonas* and *Staphylococcus* flourish in wet wounds. Strike-through (leakage) of dressings also facilitates ingress of bacteria (i.e. motile organisms), and if there is leakage then something has obviously already gone wrong [with the dressing]. Selecting the right dressing is important – not just to facilitate an optimal wound environment, but to stop bacteria getting in the wound. Airborne dispersal is also a consideration, and dressings can prevent this.

"The wound assessment process starts before you take the dressing off."

Dressings can also be useful for sequestration – particularly those that absorb and retain bacteria – reducing bioburden, impacting exo- and endo-toxins (virulence determinants) and reducing the risk of cross-infection. It is useful to compare dressings for their sequestration properties, considering binding time and capacity.

Professor White concluded by saying that wound infection risks can be minimized by controlling wound bioburden and controlling micro-organism transmission between wounds, pointing out that some dressings can facilitate infection control by binding bacteria and sequestering toxins.

In vivo **and** ***in vitro*** **biofilms have differ considerably in structure**

Professor Thomas Bjarnsholt (University of Copenhagen) presented the following: Microbiology/biofilms and wounds. What do I need to know?

Planktonic and aggregate bacteria differ. Biofilms appear everywhere that a liquid flows across a surface, and any surface (artificial or natural) is prone to colonization. Acute infections are normally caused by planktonic bacteria and are dealt with by the immune system, or can be treated with antibiotics. Biofilms are more robust, therefore more problematic. They have been around for a long time – i.e. cystic fibrosis, tuberculosis, leprosy – but our control and understanding of bacteria is now better.

Diagnostics are used to demonstrate the presence of bacteria, and debrided tissue can be used to culture them. Biofilm bacteria have to be 'released' from the biofilm to enable them be grown in culture – therefore they are difficult to detect using swabs and can provide false negatives. The bacterial distribution also varies depending on where in the ulcer the biopsy was collected.

In vivo biofilms differ in structure from those grown *in vitro* – they are flat (no 'mushroom' shapes as seen in *in vitro* cultures) and consist of small microcolonies; most biofilms in chronic infections are between 5 and 100µm in diameter. Biofilms can contain a second matrix consisting of anaerobic bacteria; as oxygen content in the wound significantly decreases below a depth of 40µm, the lower wound is a good environment for anaerobes. Antibiotics and white blood cells can attack the biofilm, but often cannot penetrate below the top layer.

There are many species in the wound environment, on average, 5.4 bacterial species per wound are seen. Micro-colonies for different species exist in close proximity but remain as

separate aggregates – dependent on nutrient availability and opportunity, and infections probably occur separately, not simultaneously. There is surely a lot of mutation going on in biofilms – therefore there is likely to be genetic variation within the biofilm.

Professor Bjarnsholt summarized by saying that there is a huge difference between *in vitro* and *in vivo* biofilms. The challenge is that there are no diagnostics and no reliable means of managing biofilms. The antimicrobials recommended for biofilm management are basic disinfectant agents (alcohol, iodine), but very high concentrations are needed to disrupt mature biofilm (i.e. more than 10µg/ml silver salts). Concentrations 100–1000 times higher than for planktonic bacteria are needed to disrupt biofilm, and they will likely only kill the outer layer. Biofilms are difficult to eradicate, but evidence for so-called 'persister' cells which are different from the others, is limited. It is likely that biofilms are just difficult to eradicate completely, therefore they re-establish themselves. We need to 'go back' and keep looking at biofilms, to study them further and see what is actually going on in chronic infections.

He highlighted that from fall 2013 the University of Copenhagen is running an online course on Bacterial Biofilms and their role in chronic diseases (go to www.biofilmcourse.ku.dk for more information), plus a 1.5 day course in June 2013.

The biochemical/cellular and microbial constituents of chronic wounds

Dr Cornelia Wiegand (Jena University Hospital) gave a presentation entitled: Slough and necrotic tissue – biochemical/cellular and microbial constituents.

She began by asking "what is slough/eschar?"

- Slough is moist dead fibrinous material – it provides an ideal medium for proliferation of bacteria
- Eschar is necrotic tissue, cell debris

The constituents in both slough and eschar are similar

Debridement is necessary in helping the wound to heal, and patient-centred concerns are important. Debridement can be used to:

- Efface excess exudate
- Expunge non-viable material and slough
- Dislodge bacterial contamination/biofilm

She made the point that: "wounding is an inevitability of life".

There are four phases of healing:

1. Hemostasis
2. Inflammation
3. Repair
4. Remodelling

Clotting leads to vascular response → inflammation leads to scar formation → epithelial healing leads to contraction → a scar remains.

Repeated trauma/infection/hypoxia/ischemia/malnutrition are all factors in chronic non-healing and can lead to chronic inflammation. Degradation of growth factors and proteases can lead to more inflammation – ending in the consequence of a chronic wound locked in the inflammatory phase.

For healing to occur it is therefore necessary to correct the adverse environment.

Chronic wounds are polymicrobial – the threshold for healing impairment is set at 10^C cfu/g tissue. The bacteria most commonly found in chronic wounds are *Proteus mirabilis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. More anaerobes are found in chronic wounds as we now have molecular-based methods to identify them. Depending on the area of the human body, you will always find bacteria. As soon as skin integrity is interrupted, the protective barrier and mechanisms provided by the skin disappears.

The wound microbiota of chronic wounds seems to be more aggressive – leading to ongoing inflammation. This indicates that there is something wrong with cell signalling in the chronic wound. The pro-inflammatory mediators PMW elastase, MMP-2 and MMP-13 are all increased in chronic wounds, compared with acute wounds. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are expressed in far higher concentrations in chronic wounds – leading to detrimental effects on human cells.

- M1 macrophages lead to cytotoxicity, tissue injury: classical pathway
- M2 macrophages lead to fibrosis and cancer: alternative pathway

In chronic wounds there is a switch from M1 to M2 macrophages. Fibroblast proliferation also decreases in chronic wounds (myofibroblasts and ECM [extracellular matrix] components), with more myofibroblasts found in chronic wounds. Abnormal ECM signalling compromises healing. Proteins from the CCN family of ECM-associated signalling proteins regulate cell adhesion, migration, proliferation, differentiation, apoptosis, survival and senescence, while deregulation of microRNAs (miRNAs) may lead to compromised tissue repair.

This leads us to consider a dynamic reciprocity model – whereby changes to the ECM will affect the cell and vice versa – in chronic wounds. In these wounds there is a failure in the normal action sequence between the cells and ECM for wound healing which leads to excessive ECM degradation. Cell inhibition derives from this degradation in growth factors or ECM, and the presence of biofilm then facilitates inflammation, leading to cells that are deficient in their signalling and reactions.

“Everything comes down to oxygen” – Dr Wiegand pointed out that the role of oxygen may have been underestimated. Lack of oxygen leads to reduced cell energy, impaired radical detoxification, decreased collagen synthesis, and loss of neutrophil killing capacity. Oxygen is firstly needed for its protective effects against invading bacteria, then for angiogenesis. NPWT can improve perfusion of oxygen to the tissues, and help the cellular matrix where deficient, as well as removing exudate and therefore negative wound factors, such as toxins.

The pattern of infection in each wound is unique – identifying this enables the practitioner to personalize treatment

Dr Randall Wolcott (Southwest Regional Wound Care Centre, Lubbock, TX) presented on: Topical and systemic antimicrobials in the management of wound biofilms – The Lubbock experience.

Dr Wolcott was introduced as a “pioneer of biofilm-based wound care”.

He made the point that taking cultures frequently doesn’t improve wound outcomes, asking “Can micro-organisms have a negative effect? ***YES***”

Medical biofilms kill approximately 500,000 people per year through chronic infection. Torres 2007 found that *Staphylococcus* tempered its virulence to avoid excessive host tissue

damage, and a marked increase (excess) of neutrophils is seen in chronic wounds. Some pathogenesis (aggressive infection) involves the bacterium breaking the cell and killing it, but other (chronic) infections exist where the bacteria does not kill the cell but blocks certain pathways, such as apoptosis – so the cell can't divide, shed or ***die***.

This is the power of a biofilm – it can reconstitute itself out of almost total annihilation. Biofilm maturity studies indicate that sharp debridement opens a time-dependent therapeutic window where the biofilm is sensitive to antimicrobial strategies.

Avoiding bad habits in wound care…

- Don't just look at the surface wound
- Most wound care is done by trial and error
- Still take cultures, but be aware that the culture model is biased towards certain bacteria (especially *Staphylococcus*)
- Wound culture has run its course…it shows a very incomplete picture of wound microbiota

Culture is subject to bacterial contamination, and can grow up minor wound contaminants. When comparing sequencing, the 'gold standard' with wound culture, the types of bacteria found varied considerably. The pattern of infection in each wound is unique; it is important to accurately identify biofilm and its components, to enable the practitioner to personalize treatment to the wound. Application of systemic antibiotics in sub-optimal doses can cause resistance – therefore the practitioner needs to apply topical antibiotics in high doses, selected by the bacterial infection pattern in individual wounds.

He commented that "topical is better than systemic" in antibiotic application, and that the practitioner needs to treat biofilm specifically as it is repetitive. Treatment may involve:

- Debridement: frequent and aggressive
- Selective biocides: silver, iodine, stains
- Anti-biofilm agents: lactoferrin, xylitol, fanasol, plant products, fatty acid gel
- Antibiotics: personalize, 'strong and long'
- Use multiple concurrent dynamic strategies.

He pointed out that his team combined biofilm based wound care with cell-based therapy for faster healing:

"Suppress the biofilm and the cells are no longer challenged. If the biofilm is what is producing the non-healing behaviour, suppress the biofilm and you should get healing."

He concluded by saying that surgeons are quick to suggest amputation in biofilm wounds due to the 'risk of sepsis' but sepsis with biofilm is a rare event, as biofilm is unsuccessful when it causes sepsis. *"You want to make it [amputation] rare".*