

Staphylococci and staphylococcal infections

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The International Symposium of Staphylococci and Staphylococcal Infections is a biennial conference that brings together clinicians who treat staphylococcal infections in the community and in hospitals, veterinary microbiologists who study staphylococcal infections in animals, and basic scientists who study pathogenesis of infection and the biology of staphylococci. Over 430 delegates from 24 countries met in the historic Assembly Rooms in Bath, UK. Sessions comprised keynote lectures along with short talks by junior investigators chosen from submitted abstracts. This article reviews several important developments in the field that were discussed at the conference.

Virulence factors

The α -toxin is the archetypal β -barrel pore-forming cytolysin that is an important virulence factor in the pathogenesis of staphylococcal infections. Despite detailed knowledge of the mechanism of toxin oligomerization and pore formation, until very recently the receptor on the surface of susceptible cells has remained elusive. Julie Wardenburg (University of Chicago, IL, USA) reported that the toxin binds to the ADAM-10 protein on the surface of susceptible cells. However the interaction is not just a precursor to pore formation and cytolytic damage, because at sublytic concentrations, the ADAM-10 metalloprotease is activated, which in turn cleaves E-cadherin at tight junctions between lung epithelial cells. In addition, intracellular signaling events triggered by the α -toxin:ADAM-10 interaction lead to loss of focal adhesion of epithelial cells to the substratum. Loosening of the attachment of epithelial cells could contribute to damage to airway tissue during staphylococcal pneumonia. Inhibition of metalloprotease activity could offer a novel target to reduce tissue damage during infection.

The hallmark of *Staphylococcus aureus* soft tissue infections is the formation of abscesses. Dominique Missiakas (University of Chicago) reported new insights into the development of abscesses by proposing a developmental program comprising a series of steps requiring the contribution of different bacterial virulence factors at each stage as the host responds to the developing infection. In addition, she provided new

information about the role of coagulase, a property that is the defining feature of the most virulent of the staphylococcal species *S. aureus*. The term coagulase-negative staphylococci is widely used to denote the less pathogenic species, such as *Staphylococcus epidermidis* and *Staphylococcus lugdunensis*. Paradoxically, until the work of Missiakas, experimental data showing that coagulase is a virulence factor have remained elusive. In fact, two *S. aureus* proteins can bind to prothrombin and activate nascent thrombin activity to cause plasma to clot *viz* the archetypal coagulase and the less well known von Willebrand factor-binding protein. Both must be inactivated for the strongest reduction in virulence allowing molecular Koch's postulates to be fulfilled for these proteins as virulence factors in murine models of infection.

Extracellular DNA & thermonuclease

Bacterial DNA is released from cells by the activity of autolysins and by a form of programmed cell death. Ken Bayles (University of Nebraska, NE, USA) reported that during development of a biofilm under flow conditions, the bacteria form towers. Gaps in the previously even aggregates are caused by lysis of groups of cells by programmed cell death. DNA that is released forms part of the biofilm structure. DNA release is required for biofilm development as reported by Alex Horswill (University of Iowa, IA, USA) and Jim O'Gara (University College Dublin, Ireland). Extracellular DNA may be required

at the earliest step of bacterial attachment to a surface and also forms part of the matrix. Mutants defective in DNA release or that overexpress nuclease are defective in biofilm.

DNA released from lysed neutrophils form a neutrophil extracellular trap for bacteria, allowing bactericidal components that are also released to act on impaled bacteria. As reported by Victor Nizet (University of California, San Diego, CA, USA) *S. aureus* extracellular DNase degrades neutrophil extracellular traps and is part of the arsenal of factors (reviewed by Jos van Strijp, University of Utrecht, The Netherlands) that help *S. aureus* evade destruction by neutrophils.

Biofilm

The ability to form biofilm is a crucial factor in the pathogenesis of infections associated with indwelling medical devices. Biofilm formation may also be important in other infections and in the commensal lifestyle of bacteria during colonization of the squamous epithelium of the nares and skin. It is becoming apparent that proteins elaborated on the surface of staphylococci promote primary attachment to surfaces and cell–cell interactions as the biofilms accumulate. Several oral and poster presentations described protein-dependent biofilm for *S. epidermidis* (Dietrich Mack, Swansea, UK) and methicillin-resistant *S. aureus* (Jim O’Gara). Specific protein–protein interactions occur with recombinantly expressed domains of the implicated surface proteins *in vitro* in conditions that mimic those pertaining in the culture as the biofilm develops. Detailed investigation of the mechanistic basis of cell aggregate formation by protein chemists and structural biologists is now possible and new approaches to inhibiting biofilm development may be feasible.

Genetic manipulation of staphylococci

Perhaps the most dramatic breakthrough reported at this meeting was in a poster presentation by Ian Monk (Trinity College Dublin, Ireland). It is difficult and often impossible to introduce plasmid DNA that has replicated in an *Escherichia coli* host into staphylococci. In order to isolate mutations in chromosomal genes by allelic exchange or by transposon insertion and to perform complementation tests, it is necessary to be able to transfer plasmids from *E. coli* to staphylococci. Most genetic work with *S. aureus* has involved transferring plasmids into a restriction-deficient mutant strain RN4220 and then moving the construct to wild-type strains for analysis. The range of hosts amenable to manipulation is confined to those strains that are closely related to laboratory strains 8325 and Newman. Monk discovered that the barrier guarding *S. aureus* from foreign DNA is a novel restriction enzyme (methylated cytosine recognition and restriction [McrR]) that recognizes cytosine-methylated DNA. RN4220 is defective in McrR. Constructed mutants of wild strains defective in McrR take up DNA efficiently. For investigators wishing to manipulate wild-type strains, plasmids isolated from a cytosine methylase (*dcm*)-deficient *E. coli* mutant can be transferred directly. Alternatively, the barrier can be bypassed by heat-shocking competent cells prior to transformation. Furthermore, many *S. epidermidis* strains have proved impervious to genetic manipulation, including the archetypal biofilm forming

strain RP62a, whose genome has been sequenced. Monk has isolated an McrR mutant of this strain, allowing genetic analysis for the first time.

Control of infection

Treatment of staphylococcal infections has been severely compromised by the evolution of strains of *S. aureus* that are resistant to multiple antibiotics (the methicillin-resistance determinant in MRSA confers resistance to all currently available β -lactam antibiotics and nosocomial strains are often resistant to several other drugs). The glycopeptide vancomycin is still the drug of choice for treating MRSA. Vance Fowler (Duke University, Durham, NC, USA) reviewed current treatment practice in the USA and showed that none of the newly introduced drugs (linezolid, tigecycline, synergid and daptomycin) approved for treating MRSA infections are superior to vancomycin. The antibiotic discovery pipeline has nearly dried up, with the more stringent criteria for regulatory approval among the difficulties that have forced pharmaceutical companies to abandon or curtail discovery programs. Fowler revealed that an improved vancomycin, televancin, and two new cephalosprins, ceftopiprole and ceftaroline, with activity against MRSA are in development. However the aspiration of ten new drugs by 2020 (‘ten by twenty’) remains just that.

Countries in Northern Europe, notably The Netherlands and Scandinavia, have kept MRSA at bay in their hospitals by enforcing a ‘search and destroy’ policy described by Marc Bonten (Utrecht University). He discussed the use of mathematical modeling of MRSA transmission in a typical hospital and revealed how intervention procedures used singly or in combination would be predicted to prevent epidemic spread. Not surprisingly, it was easier to control MRSA if the model started with a carriage rate of zero compared with, for example, 15% of personnel/patients. The widespread occurrence in the community of newly evolved strains of MRSA (community-acquired MRSA [CA-MRSA]) poses another threat to the hospital in that more patients carrying CA-MRSA are being admitted. It is impossible to prevent introduction of CA-MRSA into hospitals and it is now more difficult to prevent spread.

Stephen Harbarth (University of Geneva, Switzerland) discussed the problems associated with trying to control the spread of CA-MRSA in the community, as it has reached global epidemic proportions. The risk factors for CA-MRSA infection are different to those for hospital-acquired MRSA and are sometimes called the five Cs (crowded, contact, compromised skin, contaminated items and cleanliness [lack of]). Simple personal hygiene measures in the locker rooms of people involved in contact sport or in prisons have been successful. However, transmission in the community at large, in areas of deprivation where there is overcrowding will be very difficult.

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