Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study:
Development of long-acting antimicrobial implantable devices that prevent disabling infections, cut healthcare costs and reduce bacterial resistance.

1. Summary of the impact

The use of implantable polymeric devices is limited by infection. University of Nottingham research led to patented technology for hydrocephalus shunts that provides biomaterials with long-acting antimicrobial action. Almost 70% of shunts used annually in England now comprise our [text removed for publication] shunt, and UK usage has grown by 22% since 2008. The technology has reduced infection rates from 8.75% (2008) to 3.6% (2013), and prevents around 370 brain infections and 38 deaths in England each year. This is saving NHS England an estimated £18.4m in treatment costs each year, and generating company revenue. Furthermore, our [text removed for publication] EVD catheters for temporary relief of intracranial hypertension have reduced the rate of brain infections from 7.6% to 0.9%.

2. Underpinning research

Biomaterials-associated infection is a common complication of surgical implant devices, regardless of the biomaterial used. These infections are highly resistant to the immune system and to antimicrobials. In hydrocephalus, where treatment is by insertion of a shunt or temporary external ventricular drain (EVD), infections account for one-third of all shunt-related mortality and worsen the overall prognosis. Despite modifications in surgical technique, the incidence of cerebrospinal fluid shunt infection remains unacceptably high at 5-15%, and in EVD this can reach 25-30% of cases. Even when successfully treated, infections are associated with reduced intelligence and cognition, increased risk of seizures and psychomotor retardation.

In 1993, Professor Roger Bayston began a research programme in the Biomaterials-Related Infection Group at the University of Nottingham to address this problem. In researching appropriate antimicrobial biomaterials for shunts, we discovered that individual infecting bacteria attached to the biomaterial and developed highly adherent and resistant biofilms. We showed that eradication of biofilm bacteria requires prolonged exposure to local high antimicrobial concentrations and that this needs to be sited at the interface of bacteria and implant polymer [1]. Since antimicrobial coatings do not give sufficient duration of activity, we developed a novel process [text removed for publication] that allowed devices to be impregnated, not just coated, with antimicrobials post-manufacture. In this way, the antimicrobials remain evenly distributed in the polymer matrix as molecules rather than drug particles, giving more controlled release and improved mechanical properties. Crucially, we designed the process to enable the molecules to migrate freely through the crosslinked polymer, thus repeatedly replenishing the surface layer. The manufacturing process permitted antimicrobial devices to withstand sterilisation by autoclaving or ethylene oxide. The patented technology has been commercialised only by the University of Nottingham and is unique [2]. Studies of the mode of action of the antimicrobial biomaterial showed that bacteria attached to the polymer and were then killed. But approximately 48hrs were needed to kill all the bacteria and antimicrobial coatings are rapidly depleted by fluid flow before this time-point, hence explaining the failure of these coatings. The bactericidal activity of the [text removed for publication] shunt was found to last for 50 days using rifampicin and clindamycin, compared with three days for existing technologies. This was sufficient to avoid infection in the crucial first month after shunt implant in hydrocephalus patients. Safety studies were carried out [3] and commercialisation of the shunt by [text removed for publication] has led to clinical evaluation and use (see Section 4).

The process was further adapted to cover EVD and peritoneal dialysis catheters with a long period of infection risk and with a need for broader spectrum antimicrobial activity (4,5). In both cases, where biofilm growth occurs both in the lumen and down the outside, 80-100 days effectiveness

against a range of pathogens, including *Staphylococcus epidermidis*, MRSA, anaerobes and multi-drug-resistant Gram negative bacteria such as ESBL *E coli* and Acinetobacter, was achieved. These modifications were patent protected [2]. Our recently developed long-term urinary catheter (Fisher, Ashraf and Bayston, in preparation) is also active for three months against these pathogens, as well as against *Proteus mirabilis*, known as the scourge of catheterised spinal injuries patients.

3. References to the research

1. **Bayston R**, Ashraf W, Bhundia C. Mode of action of an antimicrobial biomaterial for use in hydrocephalus shunts. 2004 J Antimicrob Chemother; 53: 778-782. http://dx.doi.org/10.1093/jac/dkh183
2. **Bayston R.** 2007. Medical devices and methods of making medical devices. EP1804845 (W02006032904) Europe.
3. Abed WT, Alavijeh MS, **Bayston R**, Shorvon S, Patsalos PN. An evaluation of the epileptogenic properties of a rifampicin / clindamycin – impregnated shunt catheter. Br J Neurosurg 1994; 8: 725-730. http://dx.doi.org/10.3109/02688699409101187
4. **Bayston R**, Fisher LE, Weber K. An antimicrobial modified silicone peritoneal catheter with activity against both Gram positive and Gram negative bacteria. Biomater 2009; 30: 3167-3173. http://dx.doi.org/10.1016/j.biomaterials.2009.02.028
5. **Bayston R,** Vera L, Ashraf W. Activity of an Antimicrobial Hydrocephalus Shunt Catheter against Propionibacterium acnes. Antimicrob Ag Chemother 2010; 54: 5082-5085. http://dx.doi.org/10.1128/AAC.00540-10

Patents filed on this technology since 1993 - Medical devices and methods of making medical devices (Bayston, R):

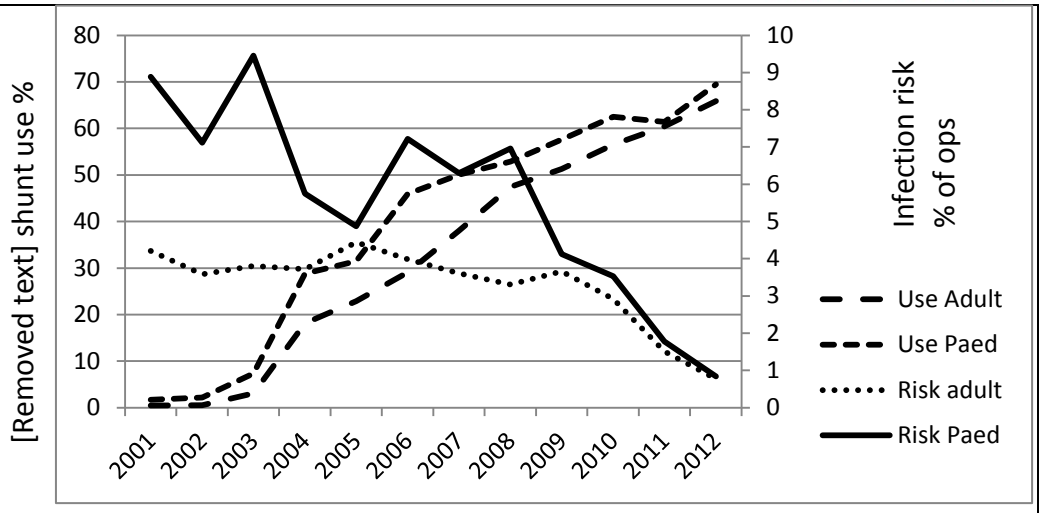
UK	0303033.5 & 0421164.5		
PCT	GB2005/003667	JP	2007-532961
Euro	05781960.9	CA	2 580 894
US	11/690 567	MYA	PI.20070453
Euro Div1	10178080.7	Euro Div2	10178073.2

4. Details of the impact

Clinical and patient benefits

[Text removed for publication] shunts and External Ventricular Drain (EVD)

The initial application of our novel approach to anti-infective catheters (USA Patent 4917686) was licensed in 1995 to a major USA company [text removed for publication]. Since launch (1998 in EU, 2001 in USA), about 97,000 children and adults in 47 countries have received the antimicrobial shunt, and since 2008 there has been a 22% growth in usage in the UK [a]. Almost 70% of shunts used annually in England now comprise our [text removed for publication] shunt [a] and the technology prevents around 370 brain infections and 38 deaths in England each year [b]. Eleven international clinical trials involving 5,613 patients [c] (2,180 since 2008) have all shown a reduction in infection (control rate 8.75%, [text removed for publication] rate 3.6%, extracted from those studies after 2008), and data from the UK Shunt Registry [J Neurosurg Pediatr 2009; 4(4): 389-393] has confirmed this. In the same analysis, infection rates for paediatric shunts were: control 5.8%, [text removed for publication] 0.9% [c]. [Text removed for publication] is currently the subject of application for regulatory approval by the Chinese FDA, in which Bayston plays a pivotal role, having face-to-face meetings with Chinese officials. In addition, the observed patient benefits of [text removed for publication] have influenced the Department of Health's National Institute for Health Research (NIHR), causing them to invest in a large multicentre clinical trial of [text removed for publication] shunts (the BASICS trial; £2.04M http://www.nets.nihr.ac.uk/projects/hta/1010430). Bayston has declined to be involved in this trial in order to avoid bias, but has given advice on diagnostic criteria and microbiological investigations.



In 2001, the technology was licensed for catheters for external ventricular drainage (EVD), a temporary means of intracranial pressure control. Since launch in 2002, 390,000 patients have benefitted from the new EVD. In 2010, we licensed our technology extending the antibacterial spectrum for EVD to cover multi-drug-resistant Gram negative bacteria such as ESBL *E coli* and Acinetobacter to [text removed for publication]. A 2010 study has shown a significant reduction in brain infection, from 7.6% to 0.9%, using [text removed for publication] EVD [d]. Use of our EVD catheter applies prophylactic antibiotics only at the site of bacterial exposure, and a 2010 study has shown that [text removed for publication] significantly reduces the need for systemic antibiotics, so reducing their adverse events including *Clostridium difficile* infection (an increasing antibiotic-related problem worldwide resulting in superinfection and often need for colectomy) [J Neurol Neurosurg Psychiatry 2010,81:1064-7]. [Text removed for publication] therefore has an important role in cutting antibiotic use and reduction of associated risk.

The current beneficiaries of the [text removed for publication] research are primarily neurosurgical patients with hydrocephalus or head trauma, who require intracranial pressure management, and who have been shown to experience significantly fewer episodes of ventriculitis, abdominal sepsis and other complications. In the US, approximately 33,000 patients are shunted each year costing $100 million [Ped Neurosurg 1995,23: 254-259]. Clinical trials of [text removed for publication] shunts since 2008 have shown a reduction in infection rate from 8.75% to 3.6% [c]. Treatment of shunt infections is by shunt removal and systemic antibiotics, and, after 2-3 weeks, insertion of a new shunt. In up to 26% of cases this needs to be repeated due to infection recurrence [J Neurosurg (Ped) 2006;105,177-181]. Therefore, applying the reduction in infection rate of 8.75% to 3.6% [c] to the 198,000 shunts inserted in USA since 2008, just over 10,000 patients would have been spared at least two, and possibly four or more, extra operations had [text removed for publication] been used throughout. Similar results (reduction in infection rate 7.6% to 0.9%) are seen when our antimicrobial EVD catheter is used in neurocritical care [d].

<u>Dialysis and urinary catheters</u>

Our modifications to the technology for other applications requiring broad antimicrobial spectrum and long duration have led to other licensing deals. The rights to our catheter for reducing peritonitis in Continuous Ambulatory Peritoneal Dialysis (CAPD) patients, with activity against staphylococci and Gram negative bacilli, were licensed to USA company [text removed for publication] in 2005, and this catheter is now undergoing CE Marking. Since 2009, the company has invested approximately $1.337M in new construction and production equipment and employed one full time engineer and two part-time regulatory / marketing executives specifically for this venture. The company have decided to name the product the ‘Bayston Catheter’ [e,f].

Beneficiaries of the CAPD catheter are those with end-stage renal disease (ESRD) who are expected to experience significantly fewer episodes of peritonitis and fewer catheter changes (each a surgical procedure). Approximately 1m people in the USA and probably several times this figure in Korea and China are affected. Worldwide, an average of 11% of ESRD patients are treated with CAPD, but in EU and Korea, CAPD is used more often, and 75% of ESRD patients in Mexico use CAPD [J Am Soc Nephrol 2012;23,533-544].

Long-term urinary catheters are used in tens of millions of patients worldwide, with infection rates around 40%. We are working with the international devices company [text removed for publication] to evaluate our recently developed urinary catheter for regulatory approval.

Training senior surgeons

The research surrounding the base technology and its clinical applications has underpinned Bayston's contributions to the DePuy Hydrocephalus and Neurocritical Care Learning Centre (http://www.depuy.com/uk/healthcare-professionals/education-and-training), held three times each year for senior professionals in Hamburg, Istanbul, Neuchatel and Prague. Since 2008, approximately 400 senior surgeons have attended, and Continuing Professional Development (CPD) points are awarded for these sessions at rates depending on national systems. As an example, a 3-day training session in Neuchatel in 2010 was attended by 61 professionals from South America, EU, Eastern Europe, Africa, Russia and Korea. Up-to-date best practice is taught and discussed so that delegates return to their home countries in a position to institute regimens to reduce complications and improve patient outcome.

Commercial benefits

Cost-savings for the NHS

One large USA [text removed for publication] shunt study [g] showed a reduction in infection rate from 12% to 3.2%, a reduction of 53 days' hospital stay for every 100 patients shunted, and an associated saving of $442,133 per 100 patients shunted. In one German hospital, use of the antimicrobial shunt catheters led to reduction in infection rate from 5.8% to 1%, yielding annual savings of $1.3m [h]. In England, the technology prevents around 370 brain infections and 38 deaths each year, thereby saving NHS England an estimated £18.4m in treatment costs annually [b]. Costs of infections vary between countries and institutions, but an estimated $100m annual cost worldwide of shunt complications (which includes non-infective causes) would be reduced by $35m-$50m by the use of [text removed for publication] shunts (calculated from figures in the literature).

5. Sources to corroborate the impact

a. Cambridge shunt registry data. Supplied in confidence by [text removed for publication]. Available on request.
b. Economic analysis by Professor R Elliott, Lord Trent Professor of Medicines and Health. The University of Nottingham.
c. Parker SL, Anderson WN, Lilienfeld S, Megerian JT, McGirt MJ. Cerebrospinal shunt infection in patients receiving antibiotic-impregnated versus standard shunts. J Neurosurg 2011; 8: 259-265. http://dx.doi.org/10.3171/2011.6.PEDS11257
d. Harrop JS, Sharan A, Ratliff J, et al. Impact of standardized protocol and antibiotic-impregnated catheters on ventriculostomy infection rates in cerebrosvascular patients. Neurosurg 2010; 67: 187-191. http://dx.doi.org/10.1227/01.NEU.0000370247.11479.B6 (pdf available on request).
e. Email correspondence from [text removed for publication]; and Gary Evans, Head of IP Management and Legal Services, BEIS, The University of Nottingham.
f. Letter from [text removed for publication], President, [text removed for publication].
g. Attenello FJ, Garces-Ambrossi GL, Zaidi HA, Sciubba DM, Jallo GI. Hospital costs associated with shunt infections in patients receiving antibiotic-impregnated shunt catheters versus standard shunt catheters. Neurosurg 2010; 66: 284-289 (pdf available on request). http://dx.doi.org/10.1227/01.NEU.0000363405.12584.4D
h. Eymann R, Chehab S, Strowitzki M, Steudel WI, Kiefer M. Clinical and economic consequences of antibiotic impregnated cerebrospinal fluid shunt catheters. J Neurosurg Pediatr 2008; 1: 444-450. http://dx.doi.org/10.3171/PED/2008/1/6/444