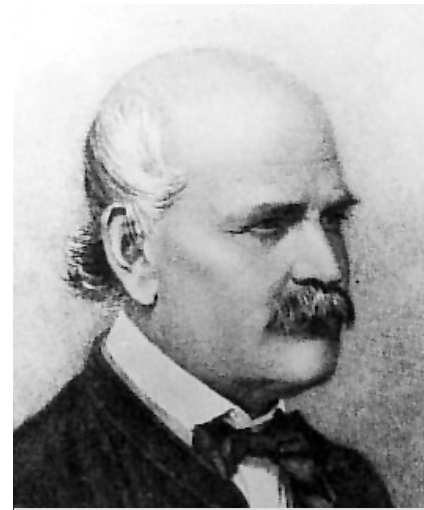


## Infectious hospitals – The dangerous side of healthcare

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**In the United States alone, approximately 2 million infections occur during treatment in a healthcare facility – infections that patients didn't bring with them and that are not related to the cause of hospitalization. The annual cost for treatment of these infections is estimated in the billions, and some 100,000 patients never go home.**

*In the 1800s, giving birth in a hospital must have been a terrifying prospect: childbed fever, also known as puerperal fever, was widespread in hospital maternity wards, with monthly mortality rates commonly topping 20% and sporadic epidemics resulting in 100% mortality of new mothers. In the 1840s, the physician Ignaz Semmelweis (1818–1865) was confounded by the very different death rates from childbed fever in his two Viennese obstetrical clinics: while annual mortality was greater than 10% in one hospital, the other had 2- to 3-fold lower rates. Semmelweis also noticed that women giving birth “on the street” – and given the death rates in the clinic, many women understandably preferred to do so – very rarely contracted childbed fever.*



Ignaz Semmelweis “I make my confession that God only knows the number of women whom I have consigned prematurely to the grave”

In the last 150 years, medicine – from our basic understanding of the human body to different ways to “fix” it – has undergone a revolution. With the latest machinery, drugs and techniques, injured patients can be rescued from the brink of death and the most seriously ill patients can often be cured.

However, despite all the advances of modern medicine, infections acquired during treatment in a healthcare facility, which may be referred to as nosocomial infections (from the Greek word *nosokomeion*: *nosos* = disease, *komeo* = to take care of), hospital-acquired infections or healthcare-associated infections, are still a common and very serious problem.

Hospitals possess characteristics that enable the spread of infection: they bring a lot of sick and/or immunocompromised individuals together, supply care personnel that move from patient to patient and provide the environment for medical procedures that bypass the body's natural protective barriers. Studies in North America and Western Europe report that 5–10% of hospitalized patients develop hospital-acquired infections. In intensive care units, where patients are even more susceptible and multiple invasive procedures (lines, catheters, ventilators) are the rule rather than the exception, 25–30% of patients are affected. The costs of hospital-acquired infections are enormous in terms of both human suffering and money, and at least one-third of these infections are estimated to be avoidable. Although the frequency of nosocomial infections has remained relatively stable over the last years, there has been an alarming increase in antibiotic resistance, narrowing treatment options and significantly contributing to the rise in deaths due to infectious disease.

## Antibiotics: salvation lost

*Childbed fever, an infection of the genital tract that can lead to septicemia or peritonitis, was the cause of approximately half of maternal deaths in the 18<sup>th</sup> and 19<sup>th</sup> centuries. Improved hygiene in the 1900s substantially reduced the incidence of disease, and the introduction of sulfonamides in the 1930s and penicillin in the 1940s dramatically decreased deaths attributable to childbed fever. Strains of *Streptococcus pyogenes* (Group A streptococcus), the bacteria most commonly responsible for childbed fever, have remained sensitive to penicillin, but the same can unfortunately not be said for many other important disease-causing bacteria.*

In 1967, the U.S. Surgeon General William H. Stewart, speaking before a panel of health officials, declared that we could “close the book on infectious diseases.” Of course it was clear that there was still work to be done, with some infections proving a bit more difficult to defeat than others, but the combined success of antibiotics (and other antimicrobials), vaccination and improved sanitation in reducing infectious disease had indeed led to a widespread feeling of optimism that infectious disease - previously the main cause of human death - was on its way out. False optimism.

After decades of decline, the threat of infectious diseases is on the rise. A host of new disease-causing microbes (*e.g.* HIV, SARS, Lyme disease) have been discovered in recent years, and many of our old foes – the ones we thought we had beaten – are showing their teeth again. The efforts to contain tuberculosis and malaria, which once looked so promising, have suffered major setbacks. And antibiotics, the wonder drugs that turned the tide against bacterial infections that had plagued humans for thousands of years, are losing effectiveness. We have underestimated the flexibility of the microbes we are fighting.

Microbes replicate quickly and are therefore able to respond rapidly to environmental pressures such as antibiotics. Penicillin-resistant *Staphylococcus* was detected in 1947, just 4 years after penicillin became widely available. Methicillin-resistant *Staphylococcus* was found within a year after release of the drug in 1960, and successive generations of cephalosporins have met the same fate. In hospitals, where antibiotic use is very high, the resistance problem is particularly serious: more than 70% of hospital-acquired infections show resistance to at least one antibiotic, and multidrug resistance is on the rise. In the past pharmaceutical research was able to keep ahead of the wave of resistance, producing new alternative antibiotics before the old ones were useless. However, things have changed.

Since the early 1990s, drug companies that had built their foundation on antibiotic research have been leaving the field, and fewer and fewer new antibiotics have been approved for use: between 1983 and 1987, the U.S. Food and Drug Administration (FDA) approved 16 new antibiotics, while only 4 were approved between 2003 and 2007. In 2006, a survey by the Infectious Diseases Society of America counted only 13 potential new antibiotics in mid- to large-scale clinical trials – which is still far away from approval for use. There is a general consensus that it has become more difficult to make new antibiotics. In the 1950s to 1970s, researchers concentrated on identifying molds that produce novel toxins (antibiotics) to kill competitors and tinkered with the active compounds to make them more effective - with enormous success - but this method seems to be played out, and novel approaches have yet to hit gold. However, money is certainly the central factor in the decline in antibiotic research and development. While there was previously a focus on the development of broad-spectrum antibiotics, which can be used to treat a wide variety of infections (and are thus more profitable), the dramatic increases in resistance due

to the use of these drugs has shown the need for narrow-spectrum antimicrobials. Yet pharmaceutical companies have little incentive to tackle the problem: the costs of developing new drugs are high, with estimates between \$110 million and \$800 million, and there is no question that drugs that treat chronic conditions (*e.g.* arthritis, diabetes, heart disease), which must be taken for a lifetime, are more profitable than a good antibiotic that clears an infection in 7–10 days.

The situation in hospitals is perilous: as levels of antibiotic resistance increase, effective alternative drugs – especially those that are convenient to administer and have few side effects – can be hard to find. The so-called “superbugs”, bacteria that are resistant against multiple antibiotics, are of particular concern. In the hospital, while bacteria bide their time on surfaces or personnel, waiting for their next opportunity to infect, they also have the chance to “swap” plasmids encoding resistance genes. The superbug MRSA (methicillin-resistant *Staphylococcus aureus*), first detected in 1961 in the UK and now found worldwide, is highly feared because it can cause so many different kinds of infections (discussed in [Perspective, October 2007](#)), but it is by far not the only superbug causing problems (see box below). Clinicians have reserved some antibiotics, such as Imipenem, a member of the powerful but very expensive and potentially toxic Carbapenem family, to treat infections with the most resistant bacteria, but resistance against these last-resort antibiotics has been reported. In other cases, “old” antibiotics such as Colistin, which were long disregarded because of their high toxicity, have been dug out of the back of the medicine chest for treatment of increasingly resistant infections.

When it comes to natural selection, microbes have an enormous advantage. The Nobel scholar Joshua Lederberg (1925–2008) wrote that in terms of responding to the selective pressures of infectious disease, “our evolutionary capability may be dismissed as almost totally inconsequential. In the race against microbial genes, our best weapon is our wits, not natural selection on our genes.” Mankind developed antibiotics, the miracle drugs that gave us the upper hand in our battle against infectious diseases, but we have ignored the problem of antibiotic resistance - evident from the earliest days of antibiotic use - for far too long. In the race between the development of resistance and the development of new drugs, the microbes are winning. However, certain changes may enable us reverse some of the damage and preserve use of the antibiotics we have.

With estimates of incorrect antibiotic treatment (wrong antibiotic, wrong dose...) as high as 50%, it is clear that more prudent use of antibiotics is necessary. Numerous studies have shown that in cases of plasmid-mediated antibiotic resistance, restricted use of the specific antibiotics decreases the frequency of resistance over time. In some cases, rotation of antibiotics has successfully decreased the percentage of antibiotic-resistant bacteria. Rotation and restricted antibiotic use implemented in combination with up-to-date analysis of actual bacterial susceptibility (antibiograms) to enable a rapid response to emerging resistance and close work with an infectious diseases specialist may be the prescription for success in battling back the wave of resistance. (As a bonus, such measures can also significantly lower costs, as antibiotics account for 20–50% of hospital drug expenditures.) When implemented in cooperation with physicians and marketed as assistance rather than control, such measures have a great chance to work...but not without effective infection control.

## Step 1. Wash Hands

*Semmelweis had no knowledge of the causative agent of the infections in his clinic; Louis Pasteur (1822–1895), the father of germ theory, identified *Streptococcus* in women with childbed fever in 1879. However, when his friend Jakob Kolletschka (1803–1847) developed the symptoms of childbed fever (and died) after nicking his hand during an autopsy of a fever victim, Semmelweis realized that the infection was being transferred on the hands of doctors. That explained the difference in the two clinics: in the first clinic, doctors and students would attend to women in the obstetrical clinic after performing autopsies (without washing hands in between), while the midwives in charge of the second clinic did not perform autopsies. After the introduction of hand washing with chlorinated lime between autopsies and examination of patients, deaths resulting from childbed fever dropped to levels comparable to those in the second clinic.*



Louis Pasteur

“A doctor is a gentleman, and a gentleman’s hands are clean.” A response to the suggestion that doctors themselves spread childbed fever, this quote seems to exemplify the prevailing attitude of the time, for despite the clear-cut success of hand hygiene in reducing the transmission of childbed fever, Semmelweis’ results, when not ignored, were met largely with skepticism or even disdain. Although Semmelweis is now considered a pioneer in hygiene and a “savior of mothers”, the last 150 years have failed to bring about the necessary changes in the hand washing habits of many physicians and other healthcare personnel.



Jakob Kolletschka

The statistics are a bit shocking: The New England Journal of Medicine reported in 1992 that despite targeted education and monitored observation, hand washing rates in an intensive care unit were as low as 30% and never went above 48%. Although hand washing is considered the single most important measure to lower the transmission of nosocomial infections, other studies have reported similarly low hand washing compliance, with average levels estimated at 40%. Education, observation and feedback, rewarding and sanctioning... all are measures that have resulted in transient improvements, but lasting results are difficult to achieve. Why is something so straightforward and rational so difficult to put into practice?

Given the demanding working environment of a hospital, where overcrowding, understaffing and heavy workloads are common, it is perhaps not surprising that hand washing sometimes falls by the wayside. Indeed, perceived rates of hand washing (those estimated by healthcare workers themselves) are much higher than actual observed rates; when there are so many tasks to perform, something as easy as hand washing might sometimes be forgotten. The widespread introduction of alcohol rubs, which are easy to use, disinfect quickly and are easier on hands than soap and water, have been moderately successful in improving hand hygiene but are not the universal solution; alcohols and other antiseptic agents are ineffective against the spread of spo-

re-forming bacteria, and it has been reported that multiplication of *Acinetobacter* actually increases in the presence of even low concentrations of alcohol. And even with alcohol rubs, compliance is still far away from 100%.

How can physicians and other healthcare professionals be effectively reminded to perform the simple measures that reduce the spread of infection? One answer sounds mundane, perhaps even ridiculous, but has been proven to be highly efficient: lists. For example, in the state of Michigan (USA), checklists were introduced in intensive care units for central lines and ventilators, two invasive procedures with high rates of nosocomial infection. The lists were simple, containing instructions known for decades and taught to every physician, but they made a huge difference: in the first 18 months, the participating hospitals almost eliminated central line infections, saving an estimated 1500 lives and 75 million dollars. The project has maintained its success for more than 4 years (for more information, see “The Checklist” under additional reading below). There was initial resistance to the checklists by physicians, nurses and administrators, who all worked in cooperation in the project, but the results are incredible. In the busy hospital environment, checklists simply help with memory recall and outline the minimal steps necessary when performing complex procedures.

Hospitals are centers of healing, places where the most seriously injured and ill patients can be treated with all modern technology has to offer. However, hospitals are also centers of infection: modern technology has not succeeded in eliminating the transfer of infection within the healthcare environment, and microbes are increasingly successful in bypassing the drugs that have allowed us to overcome them for the past 50+ years. Change is necessary, change in the way antibiotics are used and change in the hygiene behavior of healthcare personnel. Not all nosocomial infections can be prevented, but studies have shown that success is possible in the struggle against hospital-acquired infections. It's the simple things that can make the biggest difference.

## The most important pathogens accounting for nosocomial infections<sup>a</sup>)

### *Staphylococcus aureus*

- Gram-positive, cluster-forming cocci
- normal flora of humans found on nasal passages, skin and mucous membranes
- Accounts for a large percentage of hospital-associated bloodstream infections (>20%), pneumonia (>20%), skin and soft tissue infections (>45%)<sup>b)</sup>
- methicillin-resistant *S. aureus* (MRSA) widespread; MRSA strains usually resistant to all  $\beta$ -lactams as well as aminoglycosides and fluoroquinolones but remain susceptible to glycopeptides. However, reduced susceptibility to the glycopeptide antibiotic vancomycin is being increasingly reported.



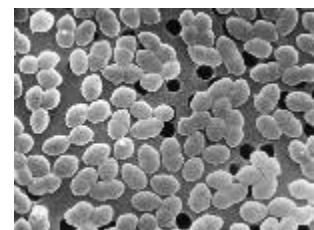
*Staphylococcus aureus*  
© HZI

### coagulase-negative Staphylococci (CoNS)

- Gram-positive, cluster-forming cocci
- normal inhabitants of skin and mucus membranes
- Involved in hospital-associated bloodstream infections (~11%), skin and soft tissue infections (~3.5%), urinary tract infections (~3.5%)<sup>b)</sup>; *S. epidermidis* most commonly identified in nosocomial infections and is known to form biofilms on (indwelling or implanted) foreign polymer bodies; other pathogenic CoNS less well characterized CoNS strains are commonly multidrug resistant

### *Enterococcus sp.*

- Gram-positive cocci, often occur in pairs or chains
- Common commensal organisms in the intestines of humans: *E. faecalis* (90–95%) and *E. faecium* (5–10%); usually has low virulence but can be a significant pathogen in weakened patients
- In hospital setting, significant cause of bloodstream infections (~10%), skin and soft tissue infections (~8%), urinary tract infections (~12%)<sup>b)</sup>
- Intrinsically resistant to  $\beta$ -lactam antibiotics and have acquired a variety of other antibiotic resistance elements. The spread of vancomycin-resistant enterococci (VRE) has complicated treatment (for *E. faecium* infection; *E. faecalis* remains largely susceptible). Rapid resistance to new antibiotics, so some VRE strains currently untreatable.



This scanning electron micrograph (SEM) depicted numbers of bacteria, which were identified as being Gram-positive *Enterococcus sp.* bacteria Photo credit: CDC/ Janice Carr

### *Klebsiella pneumoniae*

- Gram-negative encapsulated bacilli
- Klebsiellae are ubiquitous in nature and may colonize the skin, pharynx, or gastrointestinal tract
- Implicated in hospital-associated bloodstream infections (~7%), pneumonia (~8%), skin and soft tissue infections (~5%), urinary tract infections (~11%)<sup>b)</sup>
- Highly virulent strains can contain plasmids encoding extended spectrum b-lactamases (ESBLs)<sup>c)</sup> as well as AmpC type b-lactamases<sup>d)</sup>



This scanning electron micrograph (SEM) revealed some of the ultrastructural morphologic features of a *Klebsiella pneumoniae* bacterium - Photo credit: CDC/Janice Carr

### *Enterobacter sp. (E. aerogenes, E. cloacae)*

- Gram-negative bacilli
- Ubiquitous in nature
- Implicated in nosocomial bloodstream infections (~4%), pneumonia (~7%), skin and soft tissue infections (~6%), urinary tract infections (~3%)<sup>b)</sup>
- Can produce ESBLs<sup>c)</sup> as well as chromosomally encoded AmpC type b-lactamases<sup>d)</sup>

### *Escherichia coli*

- Gram-negative bacilli
- “Good” strains colonize the large intestine to the benefit of a healthy host; some virulent strains can cause serious food poisoning
- Identified in hospital-associated bloodstream infections (~18%), pneumonia (~4.5%), skin and soft tissue infections (~7%), urinary tract infections (47%)<sup>b)</sup>
- Like *K. pneumoniae*, increasingly reported to produce ESBLs<sup>c)</sup> as well as plasmid-encoded AmpC type b-lactamases<sup>d)</sup>, complicating treatment of nosocomial infection



*Escherichia coli* ©HZI

### *Pseudomonas aeruginosa*

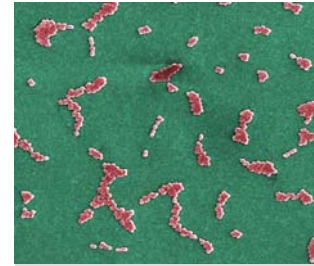
- Gram-negative bacilli
- Almost never infects healthy tissue but can infect almost any tissue if compromised in some way
- Fourth most commonly isolated nosocomial pathogen, accounting for ~10% of all hospital-acquired infections; significant involvement in pneumonia (~18%), skin and soft tissue infections (10%), urinary tract infections (7.5%)<sup>b)</sup>
- Documented resistance to every antibiotic except polymyxin B; some strains still susceptible to fluoroquinolones, gentamicin and imipenem



*Pseudomonas* ©HZI

### *Acinetobacter sp.*

- Gram-negative bacilli
- Important soil organisms, widely distributed in nature
- Of particular concern for hospital-acquired pneumonia (~3%), especially in ICUs (estimated 6–7% of ventilator-associated pneumonia caused by *Acinetobacter baumannii*, with numbers increasing); also involved in skin and soft tissue infections (~6%) and urinary tract infections (~3%)<sup>b)</sup>
- Commonly multidrug-resistant, may be resistant to carbapenems such as imipenem and meropenem



A number of clusters of aerobic Gram-negative, non-motile *Acinetobacter baumannii* bacteria - Photo Credit: Janice Haney Carr, CDC

### *Clostridium difficile*

- Gram-positive bacilli, form heat-resistant spores
- Ubiquitous in nature, particularly widespread in soil; a minor commensal bacteria of the human intestine in <3% of healthy adults but ~50% of patients with hospital stays longer than 4 weeks
- Can cause diarrhea as well as more serious conditions such as pseudomembranous colitis after antibiotic treatment eradicates normal gut flora; both frequency (doubled from 1993 to 2003) and severity of infection increasing, new epidemic strains identified
- Resistant to most antibiotics; can be treated with specific antibiotics such as vancomycin, metronidazole, bacitracin or fusidic acid



Gram-positive *Clostridium difficile* bacteria - Photo Credit: Janice Carr, CDC

### *Candida sp.*

- Yeast
- Usually live as commensals, can cause superficial infections in healthy people (*e.g.* thrush); immunocompromised individuals very susceptible to opportunistic infection
- hospital-associated *Candida* infection (largely with *C. albicans* but other species also detected) on the rise, with particular involvement in bloodstream infections and urinary tract infections
- Widely reported resistance to azoles. Can form biofilms, which exhibit resistance against most antifungal agents.



A neutrophil granulocyte interacting with a yeasts of the fungus *Candida albicans* on a collagen coated surface - Image: Dr. Manfred Rohde, HZI

### Captions:

a) Between 1990 and 1996, 34% of nosocomial infections were caused by the three most common Gram-positive bacteria (*S. aureus*, coagulase-negative staphylococci and enterococci), and 32% were caused by the four most common Gram-negative pathogens (*E. coli*, *P. aeruginosa*, *Enterobacter* spp. and *Klebsiella pneumoniae*); source: Weinstein, Robert A., Nosocomial Infection Update. Emerging Infectious Diseases. 1998. 4: 416-420.

b) Percentages (of infection in each category) based on data collected through the SENTRY Antimicrobial Surveillance Program (1997-2001)

c) ESBLs are enzymes that break the b-lactam ring, conferring bacterial resistance extended-spectrum cephalosporins with an oxyimino side chain (but not cephamycins)

d) AmpC b-lactamases confer resistance to 7-alpha-methoxy-cephalosporins (cephamycins) and are not affected by commercially available b-lactamase inhibitors

### For more information check:

[Africa](http://www.infection-research.de/fileadmin/user_upload/news/Africa.pdf) ([http://www.infection-research.de/fileadmin/user\\_upload/news/Africa.pdf](http://www.infection-research.de/fileadmin/user_upload/news/Africa.pdf))

### Additional reading:

- U.S. Congress, Office of Technology Assessment, *Impacts of Antibiotic-Resistant Bacteria*, OTA-H-629 (Washington, DC: U.S. Government Printing Office, September 1995); can be viewed on <http://books.google.com>
- Gawande, Atul, *Annals of Medicine: The Checklist* (The New Yorker); [www.newyorker.com](http://www.newyorker.com)
- *Guideline for Hand Hygiene in Healthcare Setting 2002*; [www.cdc.gov/handhygiene/](http://www.cdc.gov/handhygiene/)
- Dixon, B., *There's the rub: infection control that spreads infection* (Lancet Infect Dis 2008 8:91); Acinetobacter likes alcohol