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Lowbury Lecture

Prevention of surgical site infections: a personal odyssey

J. Kluytmans

Department of Medical Microbiology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

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The start of a long journey

I started my journey in 1988 when I was a resident in medical microbiology at the Erasmus University in Rotterdam. The head of the Department of Medical Microbiology asked me to develop a system for automated surveillance of healthcare-associated infections. We started a pilot at the Department of Cardiothoracic Surgery. The reasons for choosing this department were that we knew that there were many standardized procedures, the medical and nursing team were very co-operative and there was a relatively large amount of data available in the hospital Information System. We did not have indications that there might be specific problems at that department. Interestingly, we used a neural-network-based approach to accomplish this, thus it was a kind of artificial intelligence 'avant la lettre'.

E-mail address: jankluytmans@gmail.com.

As a reference, we started a conventional surveillance for 18 months. Of 983 patients, 38 (3.9%) developed a deep surgical site infection (SSI) [1]. These infections of the sternotomy site often had very serious consequences for the patients and more than half of them were caused by *Staphylococcus aureus*. Unexpectedly we encountered a serious patient safety issue which distracted me from the initial objective of developing an automated surveillance system. We wanted to know what was going on and started an investigation into the high rate of *S. aureus* infections. Initially we expected that there were breaks in hygienic measures or that someone was shedding *S. aureus* in the operating room. However, when we performed typing on the available *S. aureus* strains, we found that all isolates were unique. These findings did not support the hypothesis of a point source or of cross-transmission. We had no clue what the cause of this relatively high rate of *S. aureus* infections was.

An unexpected finding

At that point, a laboratory technician mentioned that they had pre-operative nasal cultures of all patients undergoing cardiothoracic surgery. Nobody could explain to me why these cultures were taken, nor who had initiated these cultures, or what was done with the results. The results ended up in a laboratory record in one of the drawers of the laboratory. Up until now, it has not become clear why this was done but for us it was a unique opportunity to determine the relation between pre-operative nasal carriage of *S. aureus* and the development of post-operative infections with that micro-organism. We started a case—control study in which cases were defined as patients who developed an *S. aureus* infection after cardiothoracic surgery. Controls were patients from the same population who did not develop an infection with *S. aureus*. Forty cases were identified, and 120 controls selected. Mortality in cases was 10.0%, compared with 0.8% in controls, confirming the seriousness of these complications. The odds ratio of pre-operative nasal carriage for cases compared with controls was 9.6 (95% confidence interval (CI): 3.9—23.7) [2].

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Thus, pre-operative nasal carriage was identified as the single most important risk factor for the development of post-surgical infections with *S. aureus*. We also performed typing on the strains from the nares and from infections and found that all pairs from individual patients were identical, whereas all patients had strains that differed from the other patients. This study clearly showed that patients were most often infected by the strains that they carried upon admission to the hospital — an exciting finding which was contrary to the existing conventions about the sources and transmission routes of *S. aureus* in surgery. As a young scientist I had the impression that I had found something new. The findings of the case—control study were presented at a national meeting of the Dutch society of medical microbiology (NVMM) and in the audience was a retired microbiologist who approached me and said that he had seen similar reports back in the '50s and '60s. These older manuscripts were not easily found in those days. There was no digitalization, so you needed to go to the libraries and search manually. If there was no lead into the topic you were looking for, in my case endogenous infections with *S. aureus*, it was almost impossible to find the relevant articles. The retired microbiologist gave me the first lead which was a manuscript from Weinstein in 1959 [3]. From that lead, about a dozen similar papers were identified performed in the '50s and '60s, which are included in a review that we published in the '90s [4]. From the existing literature, it was clear that nasal carriage was an important risk factor for patients undergoing surgery, but for unknown reasons this knowledge had been largely forgotten when I started my career in the late '80s.

S. aureus nasal carriage patterns

Nasal carriage of *S. aureus* needed to be explored in more detail and it turned out that there was an extensive amount of literature available. Cross-sectional studies had found that 25—30% of the population were carrying *S. aureus* at a given moment in time [4]. Over time, interestingly, there were three patterns of carriage which could be distinguished. Some people always carry *S. aureus* and are called persistent carriers. The majority carry *S. aureus* every now and then, with varying frequency and these are called intermittent carriers. Finally, some people never carry *S. aureus*. It is unclear what the underlying reasons are for these different carriage patterns. A study performed on healthy individuals in Rotterdam found that during a follow-up period of 10 weeks with weekly nasal cultures, approximately 50% never carried *S. aureus* [5]. Close to 20% had eight or nine out of 10 positive findings and also close to 20% had 10 out of 10 positive results. Eight years later, the available individuals with a high frequency of *S. aureus* carriage were cultured again. Ten individuals with eight or nine out of 10 positive findings were included and five of these were found to be carriers. However, none of the strains was identical to the strain found eight years earlier. There were seven individuals available who had 10 out of 10 positive findings in the initial study and all of them were carrying *S. aureus* eight years later. Three out of seven still carried the original strain. This study shows that persistent carriage is a characteristic of subset of humans and that there are certain matches between specific *S. aureus* strains and the individual. Converesely, there are individuals who seem to be 'resistant' to carriage. An interesting observation regarding this group was made in a study we performed in pig farmers [6]. This study was initiated after the discovery of meticillin-resistant *S. aureus* related to livestock and especially pigs. In the pig sties, there was an extremely high load of *S. aureus* to which pig farmers were exposed daily during work. During one year, 110 pig farmers were followed and screened for nasal carriage at days 0, 4, 7, 120, 240 and 360. At all sampling points, we found extremely high carriage rates of *S. aureus*, varying between 75% and 85% as a consequence of the extremely high exposition during work. Over the one-year follow-up period, 52% always carried *S. aureus*, 43% intermittently carried and 5% never carried *S. aureus*. This last group must have certain characteristics which makes them immune against carriage of *S. aureus*. It is unclear what makes an individual a persistent, intermittent or non-carrier. More insight into the underlying mechanisms could provide valuable knowledge to prevent *S. aureus* transmission and infections.

How to prevent endogenous infections in surgery?

Based on the findings of the case—control study and the literature review, we developed the hypothesis that perioperative eradication of nasal carriage could reduce the risk of post-surgical infections. For eradication of nasal carriage, mupirocin nasal ointment was available at that time. It was proven effective and safe. Initially we wanted to perform a randomized placebo-controlled trial in the department of cardiothoracic surgery. However, the head of cardiothoracic surgery did not support this approach as he was too concerned about the high infection rate and the consequences for the patients. Therefore, it was decided to treat all patients and the intervention was analysed as a before—after study [7]. The SSI rate dropped from 7.3% to 2.8% — a significant decline, but because of the methodological shortcomings, no firm conclusions could be drawn from this study.

Our findings initiated several randomized controlled studies to determine the effect of mupirocin nasal ointment. However, these studies included all patients irrespective of the carrier state. Overall, there were no significant effects of the intervention, but a post hoc analysis showed that in the sub-group of carriers there was a substantial reduction. A systematic review showed that in carriers the relative risk for *S. aureus* infection was 0.55 (95% CI: 0.34—0.89) whereas in non-carriers the risk ratio (RR) was 1.09 (95% CI: 0.52—2.28) [8]. Based on these studies, there were strong indications that the intervention had a protective effect for carriers, but the inclusion of non-carriers diluted the overall effect. A study in carriers only was needed to deliver more solid scientific evidence for this intervention. This approach was facilitated after the turn of the century with the development of rapid molecular tests which enabled the detection of carriers within 2 h. A multicentre, randomized, placebo-controlled trial with mupirocin nasal ointment and chlorhexidine body washings was performed in patients who had been identified as nasal carriers of *S. aureus* based on a rapid PCR result upon admission [9]. The *S. aureus* infection rate in the treated group was 3.4% compared with 7.7% in the placebo group (RR 0.42, 95% CI: 0.23—0.75) — a strong and significant effect on the primary

outcome of this study. The effect on the deep SSI-rate was even more pronounced (0.9% vs 4.4%). As part of this study, a blinded analysis of costs and benefits was performed in patients undergoing cardiothoracic procedures and orthopaedic procedures [10]. In cardiothoracic surgery, the mean cost reduction per treated carrier was €2841. In orthopaedic surgery the mean cost reduction was close to €1000. Translating this to a hypothetical hospital with 1000 procedures per year would lead to a cost savings of approximately €710,000 in cardiothoracic surgery and €250,000 in orthopaedic surgery. Also, in cardiothoracic surgery the one-year mortality rate was significantly lower in the group that was treated with mupirocin (7.6% vs 2.8%) [11]. In conclusion, peri-operative treatment of carriers with mupirocin and chlorhexidine is associated with significant (≈60%) reduction of post-operative *S. aureus* infections. The intervention is also highly cost-effective in cardiothoracic and orthopaedic surgery, and in cardiothoracic surgery it reduces one-year mortality by ≈60%.

Peri-operative treatment of nasal carriage: uptake of guidelines and situation in Europe

There are several international guidelines on the prevention of SSIs. The Centers for Disease Control and Prevention (CDC) guideline considered the topic initially but for unknown reasons it was not included in the final guideline [12]. The World Health Organization (WHO) guidelines did include the topic and made two recommendations [13]. First, the panel recommends that patients undergoing cardiothoracic and orthopaedic surgery with known nasal carriage of *S. aureus* should receive peri-operative intranasal applications of mupirocin 2% ointment with or without a combination of chlorhexidine body wash (strong recommendation, moderate quality of evidence). Second, the panel suggests considering also treating patients with known nasal carriage of *S. aureus* undergoing other types of surgery with peri-operative intranasal applications of mupirocin 2% ointment with or without a combination of chlorhexidine body wash (conditional recommendation, moderate quality of evidence). This separation is based on the level of evidence of effectiveness in different surgical procedures. The recommendations are clear and quite strong. The National Institute for Health and Care Excellence (NICE) guidelines also included nasal decontamination and gave the following recommendation: "Consider nasal mupirocin in combination with a chlorhexidine body wash before procedures in which Staphylococcus aureus is a likely cause of an SSI. This should be locally determined and take into account the type of procedure, individual patient risk factors and the potential impact of infection". Although this recommendation encourages the policy it depends fully on the local interpretation if and to what extend it is implemented [www.nice.org.uk/guidance/ng125].

It is unclear how these recommendations are implemented in clinical practice. Recently we performed a large observational study in Europe to determine the incidence and risk factors for post-surgical *S. aureus* infections (The ASPIRE-SSI study [14]). We included patients from 33 hospitals in 10 European countries. Before inclusion, patients were screened for *S. aureus* carriage, and were included based on carriage status. For every two carriers, one non-carrier was included. Finally, 5004 patients were included and 100 *S. aureus* infections were observed. The weighted cumulative incidence of *S. aureus* infections in carriers was 2.6% and in non-carriers it was 0.5%. Thus, carriers had a five-times-higher risk of developing a *S. aureus* infection. Decolonization was not performed in most of the centres and procedures.

Conclusions

Carriage is a well-recognized risk factor for *S. aureus* infections in surgical patients. The risk for carriers can be mitigated by pre-operative decolonization therapy. This preventive intervention has been studied most extensively in cardiothoracic and orthopaedic surgery. International guidelines have different interpretations and recommendations based on the available evidence. A recent European surveillance in surgical patients showed that decolonization is currently not frequently performed, and that carriage is still an important risk factor.

Knowledge gap

Although we know that the nares are the reservoir for the post-surgical infections, we do not know the exact route of transmission. In theory, there are several mechanisms through which *S. aureus* can spread from the nose to the site of infection in the operating room: (1) direct contact; (2) indirect contact; (3) haematogenous transmission; and (4) airborne transmission.

Direct contact occurs when the skin covering the surgical site harbors *S. aureus*, and from there the surgical wound becomes infected when the incision is made. It has been shown that the skin of nasal carriers is frequently colonized with *S. aureus* originating from the reservoir in the nose [15]. However, it is standard care to use antiseptic agents at the surgical site prior to surgery, which should prevent the development of infection via this route [12]. Indirect contact can play a role when, for instance, medical equipment or people in the operating room are contaminated with *S. aureus* originating from the nose of the patient, and then come into contact with the surgical site. Considering the high level of infection control and especially aseptic conditions during surgery, this transmission route is considered unlikely as a cause of *S. aureus* SSI. The third option is haematogenous transmission, which occurs when *S. aureus* enters the bloodstream while the patient is undergoing surgery. This may be caused by injury of the oropharyngeal mucosal surface during mechanical intubation. This is theoretically possible, but also considered unlikely because it is common practice to treat patients peri-operatively with antibiotic prophylaxis with good activity against *S. aureus* [16].

Finally, we consider airborne transmission as a possible route of transmission. During surgery, pathogen-loaded droplets may be dispersed from the nose and oropharynx into the air. This can occur during inhalation anaesthesia and these particles can be disseminated by air currents and remain airborne for extended periods of time. It has been shown that disturbances to the airflow in the operating room may cause displacement of airborne particles carrying bacteria to the surgical site [17]. In particular, carriers with high loads are more likely to spread *S. aureus* in their surroundings [17]. There are simulations of disturbances to the airflow in the operating room during surgery, for example, by lights, patient warming

devices and people. These disturbances cause air turbulence, and this can subsequently lead to contaminated particles being transported to the incision site. As an example, this online video shows how particles that are produced near the head of a patient, are transported to the incision site: https://youtu.be/yq-hVBjgZEk. Therefore, airborne transmission could be an important source of post-surgical infections with *S. aureus* which originate from the nares of the patient, even though we cannot exclude the other options.

In conclusion, nasal carriage of *S. aureus* is an important determinant of post-surgical infections with this micro-organism. Peri-operative eradication is associated with reduced infection rates but the uptake of this preventive measure in clinical practice is currently low. It is not clear how the infection develops from the nasal reservoir, and it is important to have better understanding of the exact route of transmission as it may lead to more effective preventive interventions.

Conflict of interest
None declared.

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