Dear Editor,
we thank the reviewer for the corrections made and the precious suggestions which certainly improve the quality of manuscript.
Following our responses to the reviewer's comments.

1) Title
I assume this is a perspective paper. It is better to clarify it in the title, such as "Air quality in the operating theatre: A perspective".

RESPONSE Thank you, we willingly accept the proposal. The title has been changed.

2) Page 1 Line 4
It is better to spell out for "HAIs" such as "hospital acquired infections (HAIs)".
RESPONSE Sorry, this had been overlooked. The “HAIs” has been written in full as "hospital acquired infections"

3) Page 1 Line 12
The term "land on" is unclear. Does that mean direct contact? Please clarify.

RESPONSE To be clearer, the same term “fall on” has been used.

4) Page 1 Line 22

The part "the SSI incidence decreased, as the SSI incidence" is unclear. Please re-write for clarity.

RESPONSE Sorry, it was a mistake; the repeat has been eliminated.

5) Page 1 Lines 23 to 28
The study compared air microbial contaminations and the surgical outcomes across the types of ventilation, i.e., turbulent vs. unidirectional. Did this study control for ventilation rates? I expect ventilation rate (air exchange rate) is more important than types of flow in reducing microbial concentrations in air. Or, unidirectional is better than turbulent if the ventilation rate is the same? Please explain more why people believe laminar flow is better than turbulent flow.

RESPONSE

We have explained the main features of unidirectional airflow system the first time it is mentioned, i.e. the higher air changes per hour and the “piston displacement” of air which leads to a significantly reduction of airborne microorganisms concentration, compared with turbulent air system.

The sentence was changed as the following, and the Charnley 1972 reference, dealing with the four phases was added:

“He constructed the first clean-air enclosure system for healthcare settings, the so-called Charnley-Howorth, and introduced the unidirectional airflow system in operating theatres (Charnley 1964), which thanks to the increased air supply volume and the “piston displacement” of air led to a very much lower concentration of airborne micro-organisms compared with turbulent airflow system. Over the four stages of Charnley's activity, the number of air changes per hour was increased up to 300 air changes/hour, and, in parallel, the levels of microbial air contamination and the SSI incidence decreased (Charnley 1972).”

We have added the Lowbury & Lidwell 1978 reference where details of the trial are reported.

6) Page 1 Line 37

What does ISPESL stand for?

RESPONSE The acronym has been clarified.

7) Page 1 Line 44

The upper-case characters should be used for "cfu" for consistency across the manuscript. Please check throughout the manuscript (e.g., Page 2 Line 17).

RESPONSE The upper-case characters have been used for “cfu” throughout the manuscript.

8) Page 2 Lines 23 and 24

I'm curious whether there are generally accepted methods and threshold values in non-European countries. If there are, please provide the information.

RESPONSE: Thank you for your question, which is difficult to be answered.

As far as we know, also on the basis of the available literature, there is no standard on air quality in operating theatres in the US, as reported by Parvizi et al (Parvizi et al, 2017); there are some recommendations in Western Australia referred to air bacterial contamination in at rest conventional and ultraclean operating theatres (2015), but we do not know in other non-European Countries. As is reported in the conclusions of our paper, in order to know the availability of guidelines on air quality in the operating theatre within the EUNETIPS (European network to promote infection prevention for patient safety) a survey is being carried out; without this survey we would not know the situation at even at a European level.

We propose to change the sentence “However, there are no generally accepted methods for air sampling nor common threshold values on microbial air contamination in European Countries.” TO “There is currently no internationally agreed standard for microbial air quality in OTs”.

Page 3 Line 11
What does T-OTs stand for?
T-OTs stands for “turbulent operating theatres”. We have added it.

10) Page 3 Line 15

"however" --> ", however,"
Thank you, the commas have been added.

11) Page 3 Line 28

I'm curious where carcinogenic smoke originates in OT.

RESPONSE:
Surgical smoke originates from devices, which produce heat, used to dissect tissue and provide haemostasis. These surgical devices include lasers, electrosurgical units, ultrasonic units, cautery units, and high speed drills and burrs.

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AIR QUALITY IN THE OPERATING THEATRE: A PERSPECTIVE

Abstract

Operating theatres are among the hospital's most risky environments as far as infections are concerned. Surgical site infection is a serious complication of surgery, associated with increased morbidity, mortality, and costs. The ambient air of the operating theatre represents an important vehicle of micro-organisms causing surgical site infection, in particular in clean operations. The aim of this paper is to give a brief historical excursus of the milestones of the prevention of airborne surgical site infections. The debated issue on the use of unidirectional airflow ventilation system is presented. Some national recommendations for threshold air microbial contamination values are reported, and the need for a European standard on air quality to provide a safe operating theatre environment for surgical patients is underlined.

Key words: operating theatre, air quality, micro-organisms.

Historical perspective

Surgical site infections (SSIs) are among the most frequent and most feared complications after surgical operations, constituting up to 19.6% of all hospital acquired infections in Europe (ECDC 2013). SSIs are associated with longer hospital stay, additional surgical procedures, higher mortality and additional costs (WHO 2016). Several factors may influence the risk of SSI development, including the type of operation, its duration, the patient's risk factors, the surgical technique, antibiotic prophylaxis, the surgical team's behavior, the environmental characteristics of the operating theatre (OT). Microbial contamination of the surgical site is a necessary precursor of the subsequent SSI. Airborne microorganisms, which mainly derive from people present in the operating theatre (Noble 1975) can enter surgical wounds by two possible routes: they can either fall directly into the wound or they can fall on exposed surfaces, as for example instruments, and surgeons' hands, surgical cloths and then be transferred into the wound. Lister is credited for having first introduced prevention practices aimed at reducing air microbial contamination, such as the spray of carbolic acid around the surgical bed to "destroy the life of the floating particles" (Lister 1909). However, the interest for the air quality in OT increased considerably with the British surgeon John Charnley who introduced the joint replacement procedures. He was convinced that the high and unacceptable rate of wound infections in joint replacements was caused by airborne microorganisms. He constructed the first clean-air enclosure system for healthcare settings, the so-called Charnley-Howorth, and introduced the unidirectional airflow system in operating theatres (Charnley 1964), which thanks to the increased air supply volume and the "piston displacement" of air led to a very much lower concentration of airborne micro-organisms compared with turbulent airflow system. Over the four stages of Charnley's activity, the number of air changes per hour was increased up to 300 air changes/hour, and, in parallel, the levels of microbial air contamination and the SSI incidence decreased (Charnley 1972).

A clear scientific confirmation of Charnley's hypothesis came from the Medical Research Council (MRC) randomised controlled trial carried out between 1974 and 1979 involving 19 hospitals and 8,055 hip and knee joint replacements performed in turbulent airflow, unidirectional airflow operating theatres and unidirectional airflow operating theatres with surgical team wearing body exhaust suits (Lowbury & Lidwell 1978; Lidwell et al, 1983); the results showed a significant correlation between air microbial contamination, surgical site contamination before closure and deep surgical site infections. Following this study, ultraclean operating theatres were recommended for hip and knee arthroplasty and microbial air contamination threshold values in the UK were

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defined for both unidirectional air flow operating theatres and for conventional operating theatres (HTM 2025). For ultraclean operating theatres, recommended values were stated both for operations with the surgical team wearing conventional clothes and wearing body exhaust suits at the patient area (<10 CFU/m^3 and <1 CFU/m^3 respectively), at the perimeter of the operating theatre (≤20 CFU/m^3, <10 CFU/m^3 respectively) and the air leaving the final diffuser (≤0.5 CFU/m^3). For conventional operating theatres, recommended values were provided for at rest (≤35 CFU/m^3) and operational conditions (≤180 CFU/m^3). These British guidelines represented the reference for the Italian ISPESL (National Institute for Occupational Safety and Prevention) guidelines, where the same threshold values for conventional operating theatres were recommended, while for ultraclean operating theatre the value of ≤20 CFU/m^3 in the operating theatre and ≤1 CFU/m^3 at the final diffuser were recommended (ISPESL 1999). In 2007 the British Health Technical memorandum was published, which superseded the previous version of Health Technical Memorandum 2025; a single value of less or equal to 10 CFU/m^3 for ultraclean theatres was recommended, and the threshold value of air microbial contamination for conventional operating theatres at rest was lowered to less or equal to 10 CFU/m^3 (HTM 03-01, 2007). The threshold value for conventional operating theatres during surgical activity remained unchanged at ≤180 CFU/m^3 (HTM 03-01). The ISPESL guidelines (ISPESL 2009) reviewed in 2009 did not change any of the recommendations given in the 1999; it was only specified that the 35 CFU/m^3 threshold value recommended for conventional operating theatres "at rest" is only indicative, since threshold values could be even lower. The French quality standard (AFNOR NORMALISATION 2013) issued in 2013 provides threshold values only in operating theatres at rest: for ultraclean operating 10 CFU/m^3 (class 3) and 1 CFU/m^3 class 4; for conventional operating theatres 10 CFU/m^3 (class 3). The Swedish guidelines (Swedish guidelines 2015), issued in the same year, do not set the air quality standards according to the type of ventilation (unidirectional or conventional), but they are set for the type of surgery: general surgery and clean infection prone surgery (e.g. implants surgery). The requirements for general surgery are 50-100 CFU/m^3, by active sampling, and 15-30 CFU/plate, by passive sampling; the requirements for infection prone surgery are 5-10 CFU/m^3 by active sampling, and no requirements for passive sampling are given. Swedish guidelines, in addition to active sampling methods, for general surgery, recommend the use of passive sampling for the evaluation of microbial air sedimentation on the critical surfaces (the surgical wound). Passive sampling was already proposed in 1999 by Swedish researchers saying that sedimentation plates are clinically more relevant than air counts of bacteria for assessment of surgical site contamination (Friberg et al, 1999). Other authors have supported the use of passive sampling, which was standardized by the Index of microbial air contamination (IMA) (Pasquarella et al, 2000) and represents the number of CFU settling on a plate of 9 cm in diameter exposed for 1 hour at a 1 m from the floor and 1 m away from obstacles; maximum value of 5 IMA and 25 IMA were recommended respectively in ultraclean and in conventional OTs. IMA standard was included in the H+ Swiss guidelines (H+, 2007) which recommended for arthroplasties target value, alert value and action value which were respectively 2, 2-5, 5 IMA, while for general surgery 15, 15-25, 25 IMA.

However, there is currently no internationally agreed standard for microbial air quality in OTs. Several studies demonstrate a high variability in microbial air contamination in the different OTs with similar forms of ventilation, suggesting the need of achieving strict control over the factors affecting air quality. Therefore, a common standard should be set and shared, to be applied in order to avoid that bad management and incorrect behavior weaken the effectiveness of preventive measures putting the patient at high risk of SSI and wasting the economic resources employed. And this is much more important in the light of the debate on the unidirectional airflow system.

The debate on unidirectional airflow system

Since the MRC study (Lidwell 1988), the use of unidirectional airflow has been recommended for hip and knee arthroplasty in many European Countries. However, it has become a subject of a great

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deal of debate since the publication in 2008 of a German retrospective study showing a significantly higher SSIs rate after hip prosthesis implantation when using unidirectional airflow ventilation compared with turbulent ventilation (Brandt et al, 2008). A subsequent meta-analysis (Bischoff 2017), performed within the framework of developing World Health Organization (WHO, 2016) Global Guidelines for the Prevention of Surgical Site Infections showed no benefit for unidirectional air flow compared with turbulent ventilation in reducing the SSI in total hip and knee arthroplasties. On the basis of this meta-analysis, the WHO Guidelines suggest that unidirectional airflow ventilation systems should not be used to reduce the risk of SSI for patients undergoing total arthroplasty surgery. However, the strength of this recommendation was considered by the expert group to be conditional, based on different factors including the level of evidence. Several criticisms have been aimed at the studies included in the meta-analysis; in particular, none of the studies had a randomized study design; most of the studies were based on large national registry databases which may not have collected information on relevant confounders; none of the study included in the meta-analysis contained an assessment of air microbial contamination. This latter point is a fundamental weakness of these studies; it should be considered that the mere presence of laminar air ventilation does not guarantee its proper function; in particular, crowding in the operating theatres and the movement of the operators, as well as the openings of the doors, can alter the flow and create turbulences, determining an increase in the air microbial contamination undermining the potential benefits of the unidirectional airflow ventilation. The study performed by the GISIO-SItI (Italian Study Group of Hospital Hygiene – Italian Society of Hygiene, Preventive Medicine and Public Health), which is the only multicentre study including the evaluation of OT air quality, showed that the recommended values for air microbial quality were exceeded in most of the air samples from unidirectional airflow OTs, challenging the belief that unidirectional system always provide acceptable airborne bacterial counts (Pasquarella et al, 2018). This study showed a lower risk of SSI, even though not statistically significant, in surgical procedures performed in unidirectional operating theatres (U-OTs) with a microbial air contamination within the recommended values (≤2 IMA and ≤10 CFU/m^3) compared with those performed in U-OTs where these limits were exceeded, and compared with those performed in turbulent operating theatres (T-OTs) with microbial air contamination recommended values for this type of OTs (≤25 IMA, ≤180 CFU/m^3).

In the light of the recent literature on the use of unidirectional airflow to reduce surgical site infections, the French Society of Hospital Hygiene stated that it is no more mandatory to use unidirectional airflow in prosthetic orthopedic surgery (SF2H 2018). It is, however, underlined that the unidirectional flow decreases the aerobiocontamination, subject to appropriate behaviors, and that it can be used in prosthetic orthopedic surgery to reduce the aerobiocontamination, and that the air quality in operating theatre depends not only on the type of airflow but also on human factors (such as number of people present, behaviour of the personnel, door openings) and highlighted the importance of performing a global risk analysis. Moreover it is said that these recommandations, developed on the basis of the knowledge available at the date of publication, are likely to evolve according to the new data. Instead, the German Society of Hospital Hygiene (DGKH), on the basis of the various critical points raised about the studies included in the meta-analysis by Bishoff et al. (Bischoff 2017), questioned that a recommendation against the use of unidirectional airflow ventilation in OT can not be issued, and recommends the use of unidirectional airflow system in OTs in accordance with the risk of the surgical procedures, considering that it is superior to conventional turbulent ventilation in reducing pathogens and particles and at removing potential carcinogenic smoke, thus protecting patients, surgeons and exposed instruments (DGKH 2018).

In the light of the current debate on the protective role of unidirectional airflow system, it appears premature to discontinue its use for arthroplasty surgery and those who consider using it should perform first an accurate local risk assessment. Further studies, possibly a randomized clinical trial, including the evaluation of microbial air contamination and other confounder variables are desirable. In this perspective a more precise guidance on how unidirectional airflows should be

designed and used is required.

Conclusions

Airborne microorganisms play a central role in the risk of SSI, in particular in clean operations. There is no doubt about the need of the ventilation system to reduce the microbial air contamination in operating theatres and prevent airborne microorganisms from entering the surgical wound. Regardless of the ventilation system installed, turbulent or unidirectional airflow, it is essential that the air cleanliness levels are consistent with the expected values with that specific ventilation system installed. This is paramount, particularly considering that, according to the current guidelines (WHO, 2016), very high risk operations, such as hip and knee replacements, may be performed in conventional OTs. It is unacceptable that avoidable risk factors which are demonstrated to be associated with the increase of microbial air contamination (e.g. the high traffic in OTs) may compromise the preventive measures aimed at providing a safe environment. Microbiological control can be a useful tool to assess air quality and identify hazardous situations, having also an important educational role. It is essential to achieve a common view and define generally accepted standards based on the scientific evidence. Within the EUNETIPS (European network to promote infection prevention for patient safety) a survey is being carried out in order to collect information regarding the availability of guidelines on air quality in operating theatres as the basis for starting a debate on this subject towards a consensus at a European level.

Acknowledgements

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