Thoracic organ transplantation may not increase the risk of bacterial transmission in intensive care units

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ABSTRACT

A transmission study was performed to investigate whether organ recipients suffer more transmissions of bacteria than do non transplanted patients. We chose enterococci for molecular typing because of their high prevalence, transmissibility, and predominance in causing nosocomial infections.

Patients staying longer than 48 h in a cardiovascular surgery Intensive care unit (ICU) were included in our one-year prospective cohort study. Enterococci identified from clinical or surveillance isolates were collected and typed by PFGE. Episodes of transmission were defined by the identification of genetically indistinguishable isolates in two or more patients who were treated during overlapping intervals or within a 9-day window period in the same ICU. Risk factor analysis was performed.

Out of 585 patients microbiological specimens were cultured from 336 patients. From 187 of these enterococci were isolated. From 81 patients 186 enterococci isolates were typed. Out of 105 different enterococci strains, 16 cluster strains were detected and 30 episodes of transmissions occurred. The transmission rate was 7.8 per 1000 patient days. No significant association was found between “being cluster member “ and “patient organ transplanted” (OR 1.5, $CI_{95\%}$ 0.58;3.98, p = 0.38) or “patient treated in a single-room only” (OR 1.06, $CI_{95\%}$ 0.36;3,12, p= 0.91), respectively. In contrast, “being cluster member” was associated with a prolonged length of stay (OR $_{\text{per additional days of stay}}$ 1.05, $CI_{95\%}$ 1.01-1.09, p< 0.01). Thoracic organ transplantation was not found to be a risk factor for bacterial transmission, but transmission was associated with a prolonged length of stay.

Keywords: Enterococci, DNA fingerprinting, transmission, solid organ transplantation, infection control

INTRODUCTION

Patients in cardiovascular intensive care units, and thoracic transplant recipients in particular, have a high risk of incurring nosocomial infections. Nosocomial infection rates between 2.6% (ventilator associated pneumonia)(Simsek et al., 2001) and 75 % (thoracic transplant recipients)(Dagan et al., 1999; Mattner et al., submitted June 2005; Simsek et al., 2001) lead to substantial morbidity, mortality, and attributable costs(Hacek et al., 1999). Transplant recipients are widely suspected to be "prone" to infections, suggesting a kind of facilitated transmission mechanism of bacteria possibly due to iatrogenic immunosuppression and perioperative antimicrobial prophylaxis. Due to their intrinsic resistance against cephalosporins, which were widely used as perioperative antimicrobial prophylaxis, enterococci were predominant in transplant recipients. Furthermore, entrococci may colonize body surfaces in a high density. To investigate this suggestion we performed a transmission study in our thoracic surgery intensive care unit using DNA fingerprinting methods. Due to the workload and costs of DNA fingerprinting procedures we decided to concentrate on one of the most frequent bacterial species: Enterococci belong to the most frequent nosocomial microorganisms in intensive care units (ICUs) (Vincent et al., 1995) and have long survival times in the inanimate environment. It is therefore suggested that enterococci were transmitted more likely than other bacteria (Lund et al., 2002; Waar et al., 2003; Wendt et al., 1998). Furthermore, enterococci were the second most frequent isolates in the studied ICU.

Nosocomial infections due to bacterial transmissions are theoretically avoidable. Hence, the investigation of transmission episodes aims directly at the theoretically avoidable part of nosocomial infections and may furthermore stimulate better infection control measures (Weist et al., 2002).

METHODS

Study design: prospective cohort study

The study was performed on a 15 bed cardiovascular ICU of a 1,300 bed university hospital. The majority of patients admitted to this ICU underwent thoracic surgery such as cardiac valve surgery, cardiac artery bypass surgery (CABG) or heart and lung transplantation. All patients staying longer than 48 hours in the period between 1 August 2001 to 31 July 2002 were included. Transplant patients were subjected to microbiological examination of throat, rectum and urine on admission and then once a week as well as in the case of clinical findings. Specimens from the non transplant patients were taken mainly if infection signs were apparent. Cephalosporins (Ceftriaxon) were given to patients undergoing CABG or valve surgery as perioperative antibiosis for at least 48 h. Perioperative antibiosis consisted of ceftriaxon, tobramycine and flucloxacilline for heart transplant recipients, and of ceftazidim, tobramycine and flucloxacilline for lung transplant recipients for at least 72 h..

For each patient, from whom enterococci isolates were typed, the following further informations were recorded: age, gender, date of admission , discharge and isolation of enterococci, underlying diseases, type of operation, treatment in single rooms, two-bed bay or five-bed-bay. Enterococci isolates were

collected prospectively and analysed later in batches of 15 to 30 strains. Therefore, no immediate feedback of typing data to the staff was feasible.

Identification of transmission episodes

All isolated enterococci were identified at the species level according to methods routinely used in the medical microbiology laboratory. Enterococci were tested for vancomycin susceptibility on Mueller-Hinton Agar. The enterococci strains from clinical as well as surveillance cultures were collected and stored at –70°C for further molecular typing. Pulsed field gel electrophoresis (PFGE) was carried out according to the method described by Murray et al. (Murray et al., 1990). Typing patterns were analyzed by the GelCompar System (*Applied Maths, Kortrijk, Belgium, version II*). Strains with Pearson correlation coefficients ≥ 80% were regarded as identical. Two or more patients sharing one identical strain were regard as a cluster. Thus membership of one patient to several clusters was not excluded. Any cluster of size k was counted as k-1 transmissions.

Data analysis

For data analysis typing information was matched with epidemiological data. In order to identify a potential episode of transmission, we took a pragmatic approach and defined a transmission episode as the identification of genetically indistinguishable isolates in two or more patients who were treated during overlapping intervals or within a defined window period in the same ICU. For this window a period of 9 days was used because this was considered appropriate in other recently published studies (Baerwolf S, 2002; Grundmann et al., 2005) and is in accordance with the results of studies investigating the survival of enterococci on environmental surfaces (Neely and Maley, 2000; Noskin et al., 1995; Wendt et al., 1998).

For the calculation of the transmission rate at the ICU during the observation period the number of episodes of transmissions was divided by the number of patient days in the ICU for the patient group investigated. The following risk factors for “being cluster member” were regarded for univariate analysis and logistic regression analysis: patient organ transplanted, length of stay and patient treated in a single-room only.

The epi info, version 6.01, software (CDC Atlanta, GA,USA) and R 1.9 were used to analyse the data. P-values less than 0.05 were considered significant.

RESULTS

In total, 585 patients with more than 48 hours ICU stay and altogether 3,851 ICU patient days were observed. From 336 patients 3,160 clinical and surveillance specimens were sent to the laboratory. This amounts to 820 microbiological investigations per 1,000 patient days. Length of stay in the ICU of transplant recipients and non transplant recipients was 21.4±19.6 days and 19±16.1 days, respectively (p=0.58). Enterococci were cultured from 187 patients. For some patients enterococci were identified

from various sites, therefore a total of 374 strains were isolated, out of which 186 (50%) of 81 patients (2.3 per patient) were available for DNA fingerprinting. None of the typed enterococci was resistant to vancomycin. 2.6 isolates per patient were typed from transplanted patients, and 2.1 isolates per patient from non transplanted patients ($CI_{95\%}$ -0.46; 1.47, p = 0.3). For characteristics of enterococci colonised patients with typing results see table I. A total of 34 out of these 81 patients (41.9%) were those with transplants of heart or lung or both. (One patient readmitted to the ICU for reasons other than a surgical procedure received a thoracic transplantation years before).

The majority of the 186 isolates typed were from throat swabs (38.7%), tracheobronchial fluid (20.9%), wound swabs (11.2%), tips of central venous catheters (9.6%), rectal swabs (7.0%), urine specimens (3.8) (Table II). Most specimens per patient were taken from throats (0.72 per patient), whereas materials such as bronchoalveolar lavage (0.29 per patient) and urine (0.09 per patient) were taken less frequntly.

Isolated enterococci of the typed specimens belonged to the following species: *E. faecalis* (89), *E. faecium* (61) and others (36) (Table III). We found 105 nonidentical enterococci strains, leading to 16 clusters involving 35 different patients. The total of “46 patients with identical strains” exceeds “35”, because 10 patients were involved in more than one cluster. 30 transmissions were determined. 23 transmissions (76.7%) occurred while the respective cluster members were placed in different rooms or bays.

The transmission rate was 7.8 per 1000 patient days. Because the investigated ICU consisted of 15 beds this was equivalent to one transmission of enterococci in 8.6 days, supposing a full capacity utilization.

The length of stay (LOS) of patients part of at least one cluster was 26.7±21.5 days compared to 14.8±11.2 days for non cluster members (p =0.004).

In a logistic regression model for the outcome “being a cluster member” and including the variables “LOS”, “patient treated in a single room only”, and “patient organ transplanted”, only the variable “LOS” was found to be an independent risk factor (OR 1.05, $CI_{95\%}$ 1.01-1.09, p= < 0.01, Table IV).

DISCUSSION

It is widely suggested that solid organ transplant recipients suffer a lot of nosocomial infections mainly due to endogenous infections facilitated by immunosuppressive therapy(Paterson et al., 1998). Hence, nosocomial infections may appear to be inevitable in this patient group. Therefore, it is difficult to stimulate infection control measures in wards with transplant recipients. An important approach to stimulating infection control measures is the demonstration of episodes of transmissions. Therefore, we performed a prospective one-year observational cohort study in a cardiovascular intensive care unit. Transmission episodes were recorded and we compared in detail transmission counts between transplant and non-transplant patients. As the marker bacterium we chose enterococci that facilitate

transmission because of their high prevalence and their environmental stability(Wendt et al., 1998; Witte et al., 1999). Furthermore, we recorded whether patients were treated in single-room, two-bed rooms or five-bed bays.

Interestingly, transplant and non-transplant recipients were involved in transmission clusters to the same extent suggesting that, contrary to common expectations, transplant recipients were not prone to transmissions. The effect of possible confounders (length of stay (LOS) in the ICU and being treated in a single room only) was tested in a logistic regression model in addition and indeed these variables were no confounders for the tested hypothesis that transplant recipients suffer more transmissions than do non-transplant recipients. However, LOS was significantly prolonged for cluster patients. But whether prolonged LOS led to more transmissions or transmissions resulted in a prolongation of LOS, or both and to which extent, can not be answered by the present study: To investigate such a potential causality, more screening cultures taken from various sites and at various times should have been available. As we concentrated on clinical specimens and routinely taken surveillance cultures from transplant recipients, both taken following the internal routine of the investigated ICU, the causality between “LOS” and transmission remains to be investigated in future studies.

The enterococci transmission rate of 7.8 per 1000 patient days was rather high compared to the transmission rate (of 10 marker bacteria) of 5 per 1000 patient days described by Bärwolf, Grundmann et al. (Baerwolf S, 2002; Grundmann et al., 2005) but more favorable compared to recently published MRSA transmission rate (18.2 per 1000 patient days for MRSA) (Cepeda et al., 2005). Furthermore, the rather high transmission rate of enterococci suggests that also vancomycin-resistant variants (VREs) were transmissible to an equal extent explaining hospital-aquired VRE epidemics (Wendt et al., 1998). Nevertheless, it should be pointed out that comparing transmission rates between different wards is problematic for many reasons: as described recently (Austin and Bonten, 1998), transmission rates are influenced by various factors such as the mean stay of patients, certain patient subgroups (proportion of critical ill patients), the ward setting (e.g. on two 10-beds ICUs the transmission rate may be different from that of one 20-beds ICU), the staff patient contact rate and staff-patient ratio (e.g. one nurse to one patient-care should lead to fewer transmissions than would one nurse for several patients), and others(Austin et al., 1999). It is obvious that transmission rates from different ICUs which differ in many of these factors can not be compared. Whether inter-hospital comparison of transmission rates leads to an improvement of infection control measures remains still to be proven. The effect of reporting transmission data of the present study (one enterococcus transmission all 8.6 days) to staff members of the ICU led to a change of hand hygiene behaviour: wearing gloves was replaced by frequent alcoholic hand disinfection for most procedures in patient care.

Most transmissions were detected from specimens of the upper respiratory tract(35 from 81 patients demonstrated identical strains, table II). This finding is consistent with recently published results(Lund et al., 2002), who showed that 17 of 20 intubated patients shared the same enterococci strains in three different clusters in the upper airways and 12 of 20 patients in the lower airways. These colonizations of the respiratory tract had been widely regarded as endogeneous before(Witte et al., 1999).

However, as indicated in table II, the representativity of study groups in transmission studies is a limiting factor. Collecting bacterial strains in bacteriological laboratories is crucial but only from a subgroup of all patients admitted to the ward bacteriological cultures were obtained. In contrast to former transmission studies, that did not present any data about the representativity nor about a possible selection bias, our data are given here to enable the reader to asses the validity of several findings (Baerwolf S, 2002; Chetchotisakd et al., 1994; Grundmann et al., 1999; Lund et al., 2002; Wendt et al., 1998): with a typing rate of 68% for throat swabs and 71% for tip of central venous catheter a reasonably complete sample was studied, whereas the typing rate of 6.1% for rectal swabs was very low. The small number of studied rectal swabs was the major reason that we had material from only 81 out of 187 enterococci-positive patients, as only 13 enterococci isolates from 148 cultured isolates were available for typing. Missing enterococci strains might have influenced our comparison of transmissions of transplants versus non-transplants. However, isolates per patient rates for the two groups did not differ significantly. Consequently, a possible transmission rate underestimation due to nontyping could have influenced both groups in the same manner.

Endemic transmissions occur predominantly in small clusters. Nevertheless outbreaks occur as well (Luginbuhl et al., 1987; Mondino et al., 2003; Stosor et al., 1999), but will not necessarily be recognized if the spreading bacterial species have a high prevalence, the possibility of an outbreak is not suspected, and no typing methods are used (Baran et al., 2002),(Waar et al., 2003). So it happened in our study, too (Cluster “A” included 7 patients; Clusters “C”,”D” and “E” included 4 patients each). If enterococci are resistant to vancomycin, quinopristin and dalfopristin, or gentamicin,
then outbreaks become apparent more easily but often so late that serious infection control problems emerge(Farr, 1998; Mellmann et al., 2000; Nelson et al., 2000).

Contrary to our initial suspicion being a transplant recipient was not detected as a risk factor for enterococci transmission. Hence, this study provides an argument that transplant recipients are no more “prone” to bacterial transmission than non-transplant patients. Furthermore, single-rooms do not seem to protect against transmission by themselves. This suggests that transmissions were caused via staff’ hands, when no adequate hand disinfection procedures had been undertaken. However, whether presenting transmission rates to the ICU staff does improve infection control measures remains still to be proven.

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Table I: Characteristics of 81 patients from whom enterococci were typed by PFGE

Patient characteristics	**N** *(years)*
Age (± SD)	*58.7±16.5*
Male gender	56 (69%)
Main underlying disease	
Coronary heart disease	24 (29.6%)
Congenital heart disease	15 (18.5%)
Aortic aneurysm	9 (11.1%)
Fibrosis of the lung	5 (6.2%)
Endocarditis	5 (6.2%)
cardiomyopathy	6 (7.4%)
Other	17 (21.0%)
Type of surgical procedure	
Lung transplant	22 (27.2%)
Heart transplant	8 (9.9%)
Combined heart-lung transplant	2 (2.5%)
Combined liver-lung transplant	1 (1.2%)
Cardiac artery bypass surgery	7 (8.6%)
Cardiac artery bypass surgery and cardiac valve surgery	13 (16.0%)
Cardiac valve surgery	9 (11.1%)
Aortic replacement and Cardiac artery bypass surgery	5 (6.2%)
Aortic replacement	4 (4.9%)
Lung resection	1 (1.2%)
Operative sternal revision	1 (1.2%)
No actual surgical procedure	8 (9.9%)
Total	**81**

- one solid organ transplant patient was readmitted to the ICU

Table II: Number of specimens, enterococci positive isolates, number of enterococci isolates typed and enterococci isolates involved in episodes of transmission according to various sites

Specimens	**Specimens sent to the lab***	**enterococci isolates***	**enterococci isolates typed**	**Enterococci isolates involved in episodes of transmission****
Rectal swab	171	148	13	7
Throat swab	177	86	72	24
Tracheo-bronchial secretion	150	45	39	7
Broncho-alveolar lavage	61	17	12	4
Tip of central venous line	145	21	18	10
Wound swab	61	13	21	5
Urine	41	13	7	2
Other	492	31	4	1
total	**1298**	**374**	**186**	**60**
Patients	**Patients with material sent to the lab**	**Enterococci positive patients**	**Patients with enterococci strains typed**	**Patients involved in transmissions (cluster members)**
	336	**187**	**81**	**35**

* only one isolate per patient and material was considered, ** only different strains per patient and material were considered

Table III: Enterococci positive isolates, number of enterococci isolates typed and enterococci isolates involved in episodes of transmission according to the Enterococcus species

Enterococci species	Number of typed isolates	Number of different PFGE-pattern	Number of different enterococci strains involved in clusters	Number of copy strains	Number of strains involved in episodes of transmission**
Enterococcus faecalis	89	67	7	22	17
Enterococcus faecium	61	25	8	36	25
Enterococcus species	36	13	1	23	4
Total	**186**	**105**	**16**	**81**	**46**

* All strains that were typed were differentiated. “Enterococci species” mean any other enterococci but *E. faecalis* or *E.faecium*

** only different strains per patient and species were considered

Table IV: Risk factor analysis for the outcome “being cluster member”

Risk factor	Univariate analysis			Logistic regression analysis		
	OR	CI_{95}	p-value	OR	CI_{95}	p-value
Length of stay (days)	3.27#	1.30;8.20#	0.009#	1.05	1.01; 1.09	<0.01
Patient organ transplanted	1.62	0.66;3.94	0.20	1.53	0.58;3.98	0.38
Patient treated in a single room only	0.75	0.27;2.08	0.39	1.06	0.36;3.12	0.91

dichotome variable “> median” tested