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Central venous catheter-associated bloodstream infection and colonisation of insertion site and catheter tip. What are the rates and risk factors in haematology patients?

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Abstract: Skin colonisation is an important source for central venous catheter (CVC) colonisation and infection. This study intended to identify risk factors for skin colonisation prior to CVC placement (baseline colonisation) and within 10 days after CVC insertion (subsequent colonisation), for CVC-tip colonisation and for bloodstream infection (BSI). Within a randomised clinical trial, data of 219 patients with haematological malignancies and inserted CVC (with a total of 5501 CVC-days and 4275 days at risk) in two university hospitals were analysed. Quantitative skin cultures were obtained from the insertion-site before CVC placement and at regular intervals afterwards. CVC-tip cultures were taken on CVC removal and data collection was performed. Statistical analysis included linear and logistic regression models. Age was an independent risk factor for colonisation prior to CVC placement (baseline colonisation). Independent risk factors for subsequent colonisation were baseline colonisation and male gender. High level of subsequent skin colonisation at the insertion-site was a predictor of CVC-tip colonisation, and a predictor of BSI.

High level of skin colonisation predicts catheter-tip colonisation and possibly subsequent infection. Sustained reduction of bacterial growth at the CVC insertion-site is therefore indispensable. Male patients are at particular risk for skin colonisation and may be a target population for additional insertion-site care before and during catheterisation.

Response to Reviewers: Please find our respond to Reviewers' Comments as an attachment.

1 Central venous catheter-associated bloodstream infection and
2 colonisation of insertion-site and catheter tip. What are the rates and risk
3 factors in haematology patients?

4
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1 Abstract

2 Skin colonisation is an important source for central venous catheter (CVC)
3 colonisation and infection. This study intended to identify risk factors for skin
4 colonisation prior to CVC placement (baseline colonisation) and within 10 days after
5 CVC insertion (subsequent colonisation), for CVC-tip colonisation and for
6 bloodstream infection (BSI). Within a randomised clinical trial, data of 219 patients
7 with haematological malignancies and inserted CVC (with a total of 5,501 CVC-days
8 and 4,275 days at risk) in two university hospitals were analysed. Quantitative skin
9 cultures were obtained from the insertion-site before CVC placement and at regular
10 intervals afterwards. CVC-tip cultures were taken on CVC removal and data
11 collection was performed. Statistical analysis included linear and logistic regression
12 models. Age was an independent risk factor for colonisation prior to CVC placement
13 (baseline colonisation). Independent risk factors for subsequent colonisation were
14 baseline colonisation and male gender. High level of subsequent skin colonisation at
15 the insertion-site was a predictor of CVC-tip colonisation, and a predictor of BSI.
16 High level of skin colonisation predicts catheter-tip colonisation and possibly
17 subsequent infection. Sustained reduction of bacterial growth at the CVC insertion-
18 site is therefore indispensable. Male patients are at particular risk for skin
19 colonisation and may be a target population for additional insertion-site care before
20 and during catheterisation.

21 22 Keywords

23 Central venous catheter; skin colonisation; quantitative skin cultures; bloodstream
24 infection; risk factors; haematology patients

1 Introduction

2 Central venous catheters (CVC) are indispensable in medical care of patients
3 receiving chemotherapy or intensive care. However, CVC use is associated with a
4 significant risk of infectious complications [1-3]. CVC-associated bloodstream
5 infection (CA-BSI) poses a serious threat to affected patients as the attributable
6 mortality may exceed 25% [4, 5]. Furthermore, BSIs are a considerable financial
7 burden for healthcare providers [4, 6-9]. Neutropenic patients are at especially high
8 risk for BSI with rates up to 14/1000 catheter days [10].

9 Most important source of microorganisms in short-term CVC-associated BSI is the
10 skin at the insertion-site [11]. Generally catheter colonisation follows the extraluminal
11 route in short-term CVC whereas the intraluminal route (e.g. via the catheter-hub) is
12 considered common in long-term CVC [11].

13 High level of skin colonisation at the insertion-site was shown to be a predictor for
14 catheter-associated BSI and, conversely, lowering the microbial burden at the
15 insertion-site reduced catheter associated BSI-rates [2]. Thus, identifying risk factors
16 associated with skin and catheter-tip colonisation can provide a framework for
17 prevention before colonisation progresses to CA-BSI. Therefore, the objective of this
18 study was to identify risk factors for skin colonisation at the insertion-site (using
19 quantitative skin cultures), catheter-tip colonisation (using CVC-tip cultures) and
20 catheter associated BSI.

21 In a recently published randomised controlled trial, use of alcohol plus octenidine to
22 disinfect the insertion-site and for CVC care led to a significant reduction in skin and

1 catheter-tip colonisation and a reduction in CA-BSIs [12]. We conducted the risk
2 factor analysis in the subgroup of haematology patients recruited in this trial [12].

3

4 **Methods**

5 **Setting and Participants**

6 Patient recruitment was carried out from 2002 through 2005 at the haematology units
7 of University Medical Center Freiburg (Freiburg, Germany; referred to as FR) and
8 University Hospital Basel (Basel, Switzerland; referred to as BS). Both institutions are
9 tertiary care facilities with 1,500 and 1,000 beds, respectively.

10 Adult inpatients scheduled to receive a non-tunnelled CVC for an expected period of
11 five or more days were asked for their informed consent. Exclusion criteria were
12 known sensitisation against the proposed antiseptics, administration of antimicrobial
13 drugs for therapy (not prophylaxis) less than one week prior to catheterisation, pre-
14 existing BSI (i.e. fever and/or other signs of infection, positive blood culture), and
15 patients with burns. In addition, patients participating in a clinical trial on other
16 antiseptics within a period of four weeks were excluded. Patients who received a new
17 catheter after the follow-up period, i.e. at earliest 30 days after removal of the first
18 catheter, were permitted to enrol again.

19 Before catheterisation, the entry site was disinfected over an area of >200 cm² for at
20 least one minute. Applied skin antiseptics were either alcohol-based or alcohol-based
21 plus 0.1% octenidine (randomly assigned, stratified by centre). After insertion, which
22 was performed under sterile barrier precautions according to a standard protocol, the
23 catheter was dressed with sterile gauze or a semi-permeable transparent dressing.

1 Skin antiseptics were also used for care of the entry site during the change of
2 dressings. Change of dressings and skin antiseptics were performed according to a
3 standard protocol in both centres.

4 Patient and catheter characteristics were recorded for each procedure in a case
5 report form (CRF). The patients' participation in the study ended with removal of the
6 CVC or stop of treatment with the assigned study medication.

7 Recorded variables for risk factor analysis were: study centre (FR, BS), age (in
8 years), gender, bone marrow or peripheral stem cell transplantation (yes, no), type of
9 transplantation (autologous, related-allogeneic, unrelated-allogeneic), hospital stay
10 prior to CVC placement (in days), insertion-site (jugular, subclavian), CVC type
11 (antimicrobial [AM] coated with chlorhexidine and silver-sulfadiazine, uncoated),
12 number of CVC lumen (1-2, 3), type of primary wound dressing (gauze,
13 semipermeable transparent dressing), duration of catheterisation (≤ 21 days, > 21
14 days), administration of AM drugs (yes, no), cytostatics via CVC (yes, no), parenteral
15 nutrition via CVC (yes, no), blood products via CVC (yes, no), neutropenia defined as
16 leucozyte count $< 1000/\text{mm}^3$ (yes, no). The influence of the factors insertion-site,
17 number of CVC lumen, primary wound dressing, and cytostatics via CVC were not
18 analysed due to their asymmetric distribution or their imbalanced distribution in the
19 study centres FR and BS. Further details on study setting and participants have been
20 previously described by Dettenkofer et al. [12].

1 Endpoints and microbiology

2 The following endpoints were investigated: (1) baseline skin colonisation, (2)
3 subsequent skin colonisation, (3) positivity of the catheter-tip (≥ 15 colony forming
4 units [CFU]) and (4) occurrence of CA-BSI

5 (1), (2) Quantitative skin cultures were obtained before insertion and at regular
6 intervals (3 ± 1 days) from a 6 x 4-cm area of skin around the catheter
7 insertion-site using a sterile template [13]. A sterile, moistened cotton
8 applicator was swabbed around the insertion-site and across the
9 surrounding 24 cm² area. The applicator was then placed in a tube
10 containing 1.0 mL of 0.01 M phosphate-buffered saline (PBS) and taken
11 to the laboratory. After vortex mixing and diluting (1:10), aliquots of 0.1
12 ml of the suspension and of the dilution and 0.01 ml of the dilution only
13 were plated onto blood agar plates. Colonies were counted after
14 incubation at 35°C for 48 h and the mean value (CFU/24 cm²) was
15 calculated.

16 (3) After removal, CVC-tip was cultured applying the roll-plate technique.
17 Colonisation was defined as ≥ 15 CFU [14]. Results were standardised
18 for a 5 cm segment of the catheter by dividing CFU count by actual
19 length of CVC-tip in cm, multiplied by five.

20 (4) CVC-associated (primary), laboratory-confirmed bloodstream infection
21 (CA-BSI)

22 4a) CA-BSI was defined according to CDC criteria [15] as:

1 Isolation of a recognised pathogen from 1 blood culture that was
2 unrelated to an infection at another site; and/or: fever, shivering, or
3 hypotension; and 1 of the following: isolation of a common skin
4 contaminant from 2 separate blood cultures that was unrelated to an
5 infection at another site, isolation of a common skin contaminant from 1
6 blood culture for patients with an intravascular device for whom a
7 physician initiated appropriate antimicrobial therapy, or a blood test
8 result positive for an antigen of a pathogen that was unrelated to an
9 infection at another site. CA-BSI was observed from CVC placement up
10 to two days after catheter removal or, in case of patient transfer to
11 another ward or hospital before catheter removal, up to two days after
12 transfer (leading to stop of treatment with the study medication). This
13 observation period was defined as days at risk.

14 4b) Catheter-related (CR)-BSI; in addition to CA-BSI, if bacterial
15 species matched between blood and catheter-tip culture.

17 **Statistical Analysis**

18 The effect of the risk factors on the endpoints (1) baseline colonisation, (2)
19 subsequent colonisation, (2) positivity of the catheter-tip, (3) occurrence of CVC-
20 associated BSI was analysed.

21 For the analysis of endpoint (1), the logarithm of the CFU value before CVC insertion
22 was calculated, and for the analysis of endpoint (2), the mean of the logarithm of the
23 CFU values measured within the first 10 days was calculated. The effect of the risk
24 factors on endpoints (1) and (2) was analysed with a linear regression model.

1 Statistical tests were performed without adjustment for multiple testing. To quantify
2 the effect, the relative difference between groups was calculated as the difference of
3 the adjusted means of the logarithm of the CFU values, transformed with the
4 exponential function, with 95% confidence interval (CI). The factors study centre,
5 age, gender, transplantation, type of transplantation, and hospital stay prior to CVC
6 placement were analysed with regard to endpoints (1) and (2). All factors were
7 examined in multivariate analyses, including all factors simultaneously in one model.
8 Additionally, the effect of endpoint (1) on endpoint (2) was analysed..

9 The effect of the risk factors on endpoints (3) and (4) was analysed with a logistic
10 regression model. The effects were tested using Wald tests without adjustment for
11 multiple testing. To quantify the effect, the odds ratio (OR) was calculated with 95%
12 CI. The factors study centre, age, gender, transplantation, type of transplantation,
13 hospital stay prior to CVC placement, CVC type, duration of catheterisation,
14 administration of AM drugs, parenteral nutrition via CVC, blood products via CVC,
15 and neutropenia, were analysed with regard to endpoints (3) and (4). All factors were
16 examined in univariate analyses, including one factor at a time. Additionally, the
17 effects of endpoints (1) and (2) on endpoints (3) and (4) were analysed, and all
18 analyses of endpoint (3) included endpoint (1) for adjustment. Multivariate analyses,
19 including more factors simultaneously in one model, were not performed because of
20 the small number of patients experiencing endpoints (3) and (4).

21 All analyses were performed in the whole study group and separately in study
22 centres FR and BS, because study centres were heterogeneous with respect to
23 some aspects of the catheterization procedure. A separate analysis of the effects of
24 the risk factors on endpoints (3) and (4) in study centre BS could not be performed,

1 because only few patients experienced endpoints (3) and (4) in centre BS. The effect
2 of CVC type was analyzed only in study centre FR.

3 All analyses were based on complete cases, i.e. patients with complete endpoint and
4 risk factor assessment.

5 In the primary analyses, no adjustment for randomized treatment was performed.
6 Sensitivity analyses including the randomized treatment for adjustment were also
7 conducted for endpoint (2). This adjustment did not change the results substantially.

8 9 **Results**

10 219 haematology patients were enrolled resulting in 5501 catheter-days and 4275
11 days at risk (table 1).

12 Jugular insertion-site was chosen in nearly all FR patients (96%) whereas BS mainly
13 chose the subclavian site (88%). FR used uncoated CVCs in 60% of cases, BS
14 exclusively chlorhexidine silver-sulfadiazine coated CVCs.

15 16 **Baseline colonisation**

17 Age was an independent risk factor for baseline colonisation with a 1.04-fold increase
18 per additional year (95% CI [1.02, 1.07], $p=0.002$). Patients in study centre BS had a
19 0.09-fold decreased baseline colonisation (95% CI [0.04, 0.20], $p<0.0001$). All results
20 are shown in table 2 a).

21 Predominant microorganisms in baseline skin swabs were coagulase negative
22 staphylococci (CNS: N=193 in 213 patients, 91%) followed by other cocci (pooling all
23 cocci except *S. aureus*, CNS, streptococci and enterococci, N=57, 27%), aerobic

1 spore forming bacteria (N=30, 14%), *Corynebacterium spp.* (N=18, 8%), streptococci
2 (N=17, 8%), *Staphylococcus aureus* (N=11, 5%), and other nonfermenting bacteria
3 (N=10, 5%).
4

5 **Subsequent skin colonisation**

6 Independent risk factor for subsequent skin colonisation was baseline colonisation
7 showing a 1.43-fold increase in CFU per logCFU at baseline (95% CI [1.23, 1.66],
8 $p < 0.0001$). Male gender showed a 2.92-fold increased subsequent colonisation (95%
9 CI [1.29, 6.64], $p = 0.011$). The separate analysis of study centres showed that this
10 gender effect was present only in study centre FR. Study centre BS showed a 0.19-
11 fold decreased risk of subsequent colonisation as compared to FR (95% CI [0.07,
12 0.52], $p = 0.001$). Unlike for baseline colonisation, age was no risk factor for
13 subsequent colonisation. All results are displayed in table 2 b).
14

15 Microorganisms in subsequent skin swabs were largely comparable to those at
16 baseline. However, moulds were not seen in baseline swabs. Predominant
17 microorganisms were CNS (N=163 in 200 patients, 82%) as predominant bacteria,
18 followed by other cocci (N=72, 36%), aerobic spore forming bacteria (N=30, 15%),
19 *Corynebacterium spp.* (N=23, 12%), streptococci (N=20, 10%), moulds (N=19, 10%),
20 and other nonfermenting bacteria (N=15, 8%).
21
22
23

1 **CVC-tip colonisation**

2 Colonised CVC-tips (≥ 15 CFU) were found in 24 cases (13.7%). 44 CVC-tips were
3 not available (e.g., contamination of tip during removal, hospital discharge with
4 catheter in place, tip not sent to laboratory), see table 1.

5 Subsequent skin colonisation was a risk factor for CVC-tip colonisation with an OR of
6 1.20 for CVC-tip colonisation per mean logCFU within 10 days after CVC insertion
7 (95% CI [1.04, 1.40], $p=0.015$). The median logCFU for skin colonisation was 4.9 in
8 patients with a colonised CVC tip, as compared to 2.0 in patients without a colonised
9 CVC tip.

10 Risk for CVC-tip colonisation in study centre BS as compared to study centre FR was
11 estimated with an OR of 0.30 (95% CI [0.08, 1.11], $p=0.07$). Patients who underwent
12 transplantation had a slightly increased risk (17.8%) vs. patients who did not undergo
13 transplantation (7.4%). In study centre FR, chlorhexidine and silver-sulfadiazine
14 coated catheters showed a slightly (non significant) reduced colonisation rate. All
15 results are shown in table 3.

16 Most frequently isolated microorganisms were CNS (N=22 in 175 patients, 13%),
17 followed by enterococci, *Corynebacterium spp.*, *S. aureus*, and *Enterobacter spp.*
18 (N=1, 1% each).

19

20 **Laboratory confirmed CA-BSI**

21 Twenty-four cases of CA-BSI occurred. The incidence density was 5.6 per 1000 days
22 at risk. In 9 patients no information on the occurrence of BSI was available.

65

1 Subsequent skin colonisation was a risk factor for CA-BSI with an OR of 1.15 for
2 CVC-tip colonisation per mean logCFU within 10 days after CVC insertion (95% CI
3 [1.02, 1.29], $p=0.028$). The median logCFU was 3.4 in patients with CA-BSI, as
4 compared to 2.3 in patients without CA-BSI.

5 Risk for CA-BSI in study centre BS as compared to study centre FR was estimated
6 with an OR of 0.21 (95% CI [1.02, 1.29], $p=0.040$). Male patients had a slightly
7 increased CA-BSI risk (14.6%) vs. female patients (6.9%), the difference was more
8 pronounced in centre FR (20.0% vs. 7.5%, OR 3.10, 95% CI [1.08, 8.90], $p=0.036$).

9 Patients who underwent transplantation had a slightly decreased CA-BSI risk (8.5%)
10 vs. patients who did not undergo transplantation (16.3%), patients with neutropenia
11 had an increased CA-BSI risk (14.3%) vs. patients without neutropenia (2.3%),
12 though not statistically significant. In the subgroup of transplanted patients, those
13 with autologous transplantation had an increased CA-BSI risk (19.2%) vs. patients
14 with related-allogeneic (2.3%) and unrelated-allogeneic transplantation (2.6%). In
15 study centre FR, patients with an AM coated CVC had a slightly increased CA-BSI
16 risk (21.0%) vs. patients with an uncoated CVC (10.0%). All results are displayed in
17 table 4.

18 Most frequently isolated microorganisms were CNS (N=9 in 210 patients, 4%),
19 followed by *Escherichia coli* (N=7, 3%), *S. aureus*, streptococci, enterococci,
20 *Enterobacter spp.* (N=2, 1% each).

21 Catheter-tip was not colonised in 18 of 24 patients with CA-BSI and in 18 patients
22 with colonised CVC-tip no BSI occurred. CR-BSI occurred in four cases (3x CNS; 1x
23 *S. aureus*). In one patient with CA-BSI caused by CNS the catheter-tip was not
24 available for analysis, in one patient with positive CVC-tip (CNS) no data on BSI were

1 available. One patient had a positive CVC-tip (CNS) and positive blood culture
2 results for *E. coli*.

4 Discussion

5 We determined CA-BSI and CVC-tip colonisation rates and examined risk factors for
6 skin and CVC-tip colonisation and CA-BSI in a haematology patient group of two
7 university medical centres. Age and study centre FR was associated with higher skin
8 colonisation at baseline before CVC placement. Male gender, baseline colonisation,
9 and study centre FR was associated with higher subsequent skin colonisation within
10 10 days after CVC placement. The CVC-tip colonisation rate was slightly higher in
11 study centre FR than in study centre BS, and increased skin colonisation within 10
12 days after CVC placement was associated with a higher CVC-tip colonisation rate.
13 Subsequent skin colonisation, autologous transplantation, and study centre FR was
14 associated with a higher CA-BSI rate.

15 Incidence density of CA-BSI was 5.6 per 1000 days at risk. CVC-tip colonisation
16 occurred in 14% (24 out of 175) of patients.

17 The major strength of this study is the standardised treatment with two alcohol-based
18 skin-antiseptics, randomized to alcohol plus octenidine vs. alcohol alone, since a
19 valid analysis of risk factors is only possible if study treatment is standardised [16].
20 Further strengths of the study are high data quality with prospective collection at two
21 study centres, prospective planning and conduct of statistical analyses by an
22 independent clinical trials center.

1 However, there are some limitations to mention. Hub colonisation was not evaluated,
2 therefore no conclusions can be made concerning this component in pathogenesis of
3 CA-BSI. Study centres were free of choice for variables like insertion-site (which
4 varied considerably), dressing, CVC type. Thus, some variables had to be excluded
5 from statistical analysis due to asymmetric distribution. Standardised protocols
6 concerning CVC placement and insertion-site care were established but compliance
7 was only controlled on planned dressing changes with skin swabs conducted by
8 study assistants. CVC insertion itself and unscheduled dressing changes were not
9 observed continuously. Despite accurate standards for skin swabs and laboratory
10 work, involvement of different study assistants in two centres could possibly create
11 variations in results. The results on CVC-tip colonisation and occurrence of CA-BSI
12 are based on small numbers of the corresponding events, and must be interpreted
13 with some caution.

15 **Skin colonisation**

16 There are few trials published evaluating risk factors for skin colonisation at the CVC
17 insertion-site. Duration of catheterisation, male gender, age, jugular insertion-site,
18 non-compliance with maximal sterile barrier precautions, transparent dressing and
19 hub colonisation were found to be risk factors for skin colonisation [17, 18]. In our
20 trial, age was a risk factor for baseline colonisation but did not show a further effect
21 on subsequent colonisation being adjusted for baseline colonisation. Moro et al.
22 showed an effect of age only if a transparent dressing was used [17]. Once a CVC is
23 in place effects of skin antiseptics and dressings are most likely to outreach age-

1 related changes in skin characteristics (like less fat content, elasticity and moisture)
2 [19] and their effects on skin microflora.

3 Male gender was an independent risk factor for baseline and subsequent
4 colonisation. Beard growth reduces adherence of wound dressing materials in male
5 patients and increases the risk of contamination as does shaving. Both Moro et al.
6 [17] and Carrer et al. [18] found male gender to be a risk factor for skin colonisation,
7 but Moro et al. [17] could show this only for jugular access. In the separate analysis
8 of study centres, we found the effect of male gender only in centre FR and not in
9 centre BS. If the distribution of insertion sites is taken into account, this strongly
10 supports the finding of Moro et al. [17], as jugular insertion site was chosen in 99% of
11 male patients in centre FR and in only 17% in centre BS. In addition, male gender
12 was associated with higher risk for CA-BSI (which was more pronounced in centre
13 FR). Current guidelines recommend weighing up infectious vs. non-infectious
14 complications for subclavian vs. jugular access [20]. Our findings support giving
15 preference to subclavian insertion site especially in male patients.

16 Baseline colonisation itself was an independent risk factor for subsequent
17 colonisation. This finding highlights the importance of adequate initial skin
18 disinfection. In highly colonised patients, reduction of bacterial density on the
19 insertion-site could possibly be less effective than in initially less colonised patients.
20 This could facilitate faster re-growth in these patients.

21

22 **CVC-tip colonisation and CA-BSI**

23 As CR-BSI is a relatively rare event, CVC-tip colonisation is often used as surrogate
24 parameter showing good correlation with CR-BSI [21]. In our trial 18 patients with

1 CVC-tip colonisation did not develop a CA-BSI. 18 of 24 patients with CA-BSI had no
2 CVC-tip colonisation suggesting limited sensitivity of CVC-tip culture or additional
3 mechanisms in BSI development in our patient group.

4 The CVC-tip colonisation rate of 14% in our trial is within the range (2.3-37.8%) of
5 previously reported rates [22-24]. However, these data were not derived from
6 haematology patients.

7 In the subgroup of transplanted patients, those with autologous Tx had an
8 extensively higher BSI risk. This is not concordant with the literature. A recent
9 analysis of 1,699 patients found no significant differences in BSI rates between
10 different Tx types [25]. In our trial, a much smaller patient group was investigated.
11 Other factors might have influenced this result especially as no multivariate analysis
12 could be performed.

13 In our trial subsequent skin colonisation was associated with CVC-tip colonisation
14 which was also shown in a recent trial [22] and fits in with colonisation most likely
15 starting extraluminal at the insertion-site in short term CVC [11]. Subsequent skin
16 colonisation was also associated with a higher risk for CA-BSI. Initial skin antiseptic
17 and insertion-site care should intend maximal suppression of microbial growth and
18 re-growth. Antiseptics containing remanent agents (e.g. octenidine dihydrochloride,
19 chlorhexidine) should therefore be preferred due to their ability of prolonged
20 reduction of microbial growth [12]. Consistently, current US and UK guidelines
21 recommend chlorhexidine/alcohol as first-line antiseptic [20, 26]. Application of
22 sponges containing remanent antiseptic agents on CVC insertion-site is a promising
23 option for infection prevention as recently published data showed [27, 28]. As a high

1 risk group, haematology patients could benefit from such interventions. This is also
2 supported by our findings.

3 Results of routine skin cultures as an option for identifying patients at high risk for
4 BSI, as Bouza et al. showed in cardiac surgery ICU patients [29] could be used for
5 targeted additional preventive measures.

6 Results regarding chlorhexidine and silver-sulfadiazine coated CVC were
7 inconsistent showing a trend to lower CVC-tip colonisation rates but a trend to higher
8 CA-BSI-rates in centre FR.

9 Incidence density of CA-BSI (5.6/1,000 days at risk) was lower compared to
10 surveillance-data derived from neutropenic patients undergoing HCT (14/1,000
11 neutropenic days) [10]. This seems plausible, as most nosocomial infections in this
12 patient group occur during neutropenia [30] and we investigated both the neutropenic
13 and non-neutropenic phase, showing neutropenia as a risk factor for CA-BSI.

14 15 **Influence of study centre**

16 Noticeable differences in outcome variables were found between study centres.
17 Study centre FR was associated with baseline and subsequent skin colonisation,
18 CVC-tip colonisation, and CA-BSI. Choice of CVC insertion-site showed a
19 conspicuous difference between centres (subclavian: 88% BS vs. 4% FR).
20 Disregarding this fact, patients in centre FR had higher colonisation rates on both
21 insertion-sites compared to BS (median logCFU jugular/subclavian: FR 2.9/3.2; BS
22 1.6/0.0). This leads to conclude that other factors must also contribute to this effect.
23 In spite of established standards, involvement of different study assistants for skin

1 swabs could possibly affect results, as some variables (e.g. pressure exerted while
2 swabbing) are hard to standardise.

3 Preference of subclavian insertion-site in BS could have had an influence on CA-BSI
4 rates. In several previous trials the subclavian site was shown to have lower infection
5 and CVC-tip colonisation rates and is recommended in recent guidelines for infection
6 prevention [26, 31-35]. Differences in nurse staffing which were not evaluated could
7 be a further possible influencing factor. Care of CVC patients by “float” nurses was
8 previously shown to be a risk factor for BSI [36].

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Table 1: Patient characteristics

		total		Haematology FR		Haematology BS	
		n	% [#]	n	% [#]	n	% [#]
patients		219	100	154	70.3	65	29.7
randomized treatment	alcohol	109	49.8	77	50.0	32	49.2
	alcohol-octenidine	110	50.2	77	50.0	33	50.8
age	-49	102	46.6	64	41.6	38	58.5
	50-59	65	29.7	46	29.9	19	29.2
	60-69	38	17.4	32	20.8	6	9.2
	70-	14	6.4	12	7.8	2	3.1
	min/max median	18/81 51		20/81 52		18/78 48	
gender	female	93	42.5	69	44.8	24	36.9
	male	126	57.5	85	55.2	41	63.1
transplantation (PBSCT/BMT)	yes	137	62.6	98	63.6	39	60.0
	no	82	37.4	56	36.4	26	40.0
type of transplantation	unrelated-allogeneic	41	29.9	32	32.7	9	23.8
	related-allogeneic	47	34.3	24	24.5	23	59.0
	autologous	49	35.8	42	42.9	7	17.0
hospital stay before CVC placement (days)	0	44	20.1	32	20.8	12	18.5
	1	91	41.6	73	47.4	18	27.7
	2-4	52	23.7	36	23.4	16	24.6
	5-	32	14.6	13	8.4	19	29.3
insertion-site	jugular	154	71	147	96.1	7	10.9
	subclavian	63	29	6	3.9	57	89.1
	unknown	2		1		1	
CVC type	AM coated*	126	58.1	62	40.5	64	100.0
	uncoated	91	41.9	91	59.5	0	0.0
	unknown	2		1		1	
CVC lumen	1-2	6	2.8	0	0.0	6	9.4
	3	211	97.2	153	100.0	58	90.6
	unknown	2		1		1	
primary wound dressing	gauze	205	94.9	152	99.4	53	84.1
	transparent	11	5.1	1	0.7	10	15.9
	unknown	3		1		2	
CVC in situ (days)	≤21	103	48.6	70	47.0	33	52.4
	>21	109	51.4	79	53.0	30	47.6
	unknown	7		5		2	
	min/max	0/120		4/120		0/114	
	median	22		22		21	
antibiotics via CVC	yes	157	76.2	110	73.3	47	83.9
	no	49	23.8	40	26.7	9	16.1
	unknown	13		4		9	
cytostatics via CVC	yes	196	95.1	144	96.0	52	92.9
	no	10	4.9	6	4.0	4	7.1

	unknown	13		4		9	
parenteral nutrition via CVC	yes	108	52.4	78	52.0	30	53.6
	no	98	47.6	72	48.0	26	46.4
	unknown	13		4		9	
blood products via CVC	yes	165	80.1	121	80.7	44	78.6
	no	41	19.9	29	19.3	12	21.4
	unknown	13		4		9	
Neutropenia (leucozyte count <1000/mm ³)	yes	162	78.6	119	79.3	43	76.8
	no	44	21.4	31	20.7	13	23.2
	unknown	13		4		9	
baseline colonisation (logCFU)	min/max	0/13.3		0/13.3		0/9.9	
	median	6.8		7.1		5.1	
	unknown	6		0		6	
subsequent skin colonisation (logCFU)	min/max	0/14.0		0/14.0		0/11.5	
	median	2.4		2.9		0	
	unknown	19		9		10	
CVC-tip colonisation (≥ 15 CFU)	positive	24	13.7	21	17.5	3	5.5
	negative	151	86.3	99	82.5	52	94.5
	unknown	44		34		10	
laboratory confirmed BSI	yes	24	11.4	22	14.5	2	3.4
	no	186	88.6	130	85.5	56	96.6
	unknown	9		2		7	

CVC: central venous catheter; AM: antimicrobial; PBSCT: peripheral blood stem cell transplantation; BMT: bone marrow transplantation; log: logarithmised; CFU: colony forming unit; BSI: bloodstream infection.

#for all variables except min/max and median values

* chlorhexidine and silver sulfadiazine

Table 2: Risk factors for skin colonisation

a) Baseline skin colonisation (prior to CVC placement)

multivariate analysis	multiplicative effect	95% CI	p-value
all patients (n=213)^a			
study centre BS	0.09	0.04-0.20	<0.0001
age (cont.)	1.04	1.02-1.07	0.002
male gender	1.80	0.86-3.73	0.12
transplantation	0.77	0.37-1.62	0.49
hospital stay before CVC placement (cont.)	0.98	0.93-.04	0.50
only centre FR (n=154)			
age (cont.)	1.04	1.01-1.07	0.011
male gender	1.48	0.64-3.44	0.36
transplantation	1.09	0.45-2.63	0.85
hospital stay before CVC placement (cont.)	0.99	0.94-1.05	0.80
only centre BS (n=59)^b			
age (cont.)	1.05	0.99-1.11	0.076
male gender	3.05	0.67-13.9	0.14
transplantation	0.38	0.09-1.65	0.19
hospital stay before CVC placement (cont.)	0.91	0.74-1.13	0.38

^a no baseline skin sample was available in 6 patients.^b no baseline skin sample was available in 6 patients

CVC: central venous catheter; CI: confidence interval; cont.: continuous variable; BS: Basel.

b) Subsequent skin colonisation (until 10 days after CVC placement)

multivariate analysis	multiplicative effect	95% CI	p-value
all Patients (n=199)^a			
study centre BS	0.19	0.04-0.20	<0.0001
age (cont.)	0.98	0.95-1.01	0.16
male gender	2.92	1.29-6.64	0.011
transplantation	0.82	0.36-1.88	0.64
hospital stay before CVC placement (cont.)	1.00	0.95-1.06	0.91
baseline colonisation (cont.)	1.43	1.23-1.66	<0.0001
only centre FR (n=145)^b			
age (cont.)	0.98	0.95-1.02	0.31
male gender	4.15	1.54-11.2	0.005
transplantation	0.90	0.32-2.51	0.84
hospital stay before CVC placement (cont.)	1.01	0.95-1.08	0.72
baseline colonisation (cont.)	1.53	1.27-1.85	<0.0001
only centre BS (n=54)^c			
age (cont.)	0.96	0.92-1.01	0.13
male gender	0.92	0.22-3.84	0.90
transplantation	0.63	0.16-2.42	0.49
hospital stay before CVC placement (cont.)	0.89	0.74-1.08	0.24
baseline colonisation (cont.)	1.23	0.97-1.56	0.08

CVC: central venous catheter; CI: confidence interval; cont.: continuous variable; BS: Basel.

^a no subsequent skin sample or baseline skin sample was available in 20 patients.

^b no subsequent skin sample or baseline skin sample was available in 9 patients

^c no subsequent skin sample or baseline skin sample was available in 11 patients

Table 3: Risk factors for CVC tip colonisation

univariate analysis	all patients (n=174) ^a			only centre FR (n=120) ^a		
	OR	95% CI	p-value	OR	95% CI	p-value
study centre BS	0.30	0.08-1.11	0.071			
age (cont.)	0.99	0.96-1.02	0.62	0.99	0.95-1.02	0.39
male gender	1.32	0.53-3.30	0.55	1.58	0.58-4.26	0.37
transplantation	2.71	0.96-7.67	0.060	2.15	0.73-6.34	0.17
type of transplantation (106/75)						
unrelated-allogeneic	1.00		0.50	1.00		0.41
related-allogeneic	0.59	0.17-2.04		0.89	0.22-3.60	
autologous	0.49	0.14-1.67		0.43	0.11-1.63	
hospital stay before CVC placement (cont.)	0.96	0.85-1.10	0.57	0.99	0.90-1.08	0.74
CVC type AM coated ^b				0.69	0.25-1.86	0.46
CVC in situ ≤21 days	0.69	0.29-1.67	0.41	0.67	0.26-1.77	0.42
antibiotics via CVC (169/117)	1.35	0.43-4.29	0.61	2.02	0.54-7.49	0.29
parenteral nutrition via CVC (169/117)	0.70	0.28-1.78	0.45	0.65	0.24-1.75	0.39
blood products via CVC (169/117)	0.68	0.23-2.05	0.48	0.63	0.18-2.17	0.46
neutropenia (169/117)	1.49	0.41-5.41	0.55	2.03	0.43-9.56	0.37
baseline colonisation	1.09	0.94-1.28	0.26	1.04	0.87-1.25	0.67
subsequent skin colonisation (165/114)	1.20	1.04-1.40	0.015	1.18	1.00-1.40	0.046

CVC: central venous catheter; OR: Odds ratio; CI: confidence interval; cont.: continuous variable; BS: Basel; FR: Freiburg; AM: antimicrobial.

^a Exceptions in numbers of patients included in analyses are indicated in left column as number of analysed patients in parentheses (all patients/only centre FR). Patients excluded from analysis if catheter-tip was not available, or baseline skin sample was not available, or risk factor was missing

^b chlorhexidine and silver-sulfadiazine

Table 4: Risk factors for catheter-associated BSI

univariate analysis	all patients (n=210) ^a			only centre FR (n=152) ^a		
	OR	95% CI	p-value	OR	95% CI	p-value
study centre BS	0.21	0.05-0.93	0.040			
age (cont.)	0.98	0.95-1.01	0.18	0.98	0.94-1.01	0.11
male gender	2.31	0.88-6.10	0.089	3.10	1.08-8.90	0.036
transplantation	0.48	0.20-1.12	0.090	0.53	0.21-1.32	0.17
type of transplantation (130/96)						
unrelated-allogeneic	1.00		0.020	1.00		0.048
related-allogeneic	0.88	0.05-14.6		1.30	0.08-22.0	
autologous	9.00	1.09-74.6		8.44	1.01-70.7	
hospital stay before CVC placement (cont.)	0.76	0.56-1.04	0.084	0.67	0.44-1.04	0.072
CVC type AM coated ^b				2.39	0.95-6.00	0.064
CVC in situ ≤21 days (204/147)	1.32	0.56-3.11	0.52	1.19	0.48-2.95	0.70
antibiotics via CVC (205/149)	2.39	0.68-8.37	0.17	2.60	0.73-9.33	0.14
parenteral nutrition via CVC (205/149)	1.09	0.47-2.57	0.84	1.15	0.46-2.84	0.77
blood products via CVC (205/149)	1.86	0.53-6.57	0.33	1.63	0.45-5.93	0.46
neutropenia (205/149)	7.16	0.94-54.6	0.057	6.49	0.84-50.3	0.073
baseline colonisation (209/152)	1.07	0.92-1.24	0.40	1.02	0.86-1.21	0.82
subsequent skin colonisation (200/145)	1.15	1.02-1.29	0.028	1.12	0.98-1.28	0.10

CVC: central venous catheter; OR: Odds ratio; CI: confidence interval; cont.: continuous variable; BS: Basel; FR: Freiburg; AM: antimicrobial.

^a Exceptions in numbers of patients included in analyses are indicated in left column as number of analysed patients in parentheses (all patients/only centre FR). Patients excluded from analysis if data on BSI or risk factors were missing

^b chlorhexidine and silver-sulfadiazine

Ref.: Ms. No. AOHE-D-10-00015

Central venous catheter-associated bloodstream infection and colonisation of insertion-site and catheter tip. What are the rates and risk factors in haematology patients?
Annals of Hematology

Dear Dr. Luft,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

The reviewers' comments can be found at the end of this email or can be accessed by following the provided link.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by 21-05-2010.

To submit a revision, go to <http://aohe.edmgr.com/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely
Arnold Ganser, M.D.
Editor-in-Chief
Annals of Hematology

Reviewers' comments:

Reviewer #1: Title:

Adequate

Abstract:

Adequate

Introduction:

Adequate

Methods:

Adequate

Results:

1.1.

Para on Subsequent skin colonization: moulds increase from zero to 10%, please rephrase "Microorganisms in subsequent skin swabs were comparable to those at baseline"

Rephrased as follows:

Microorganisms in subsequent skin swabs were largely comparable to those at baseline. However, moulds were not detected in baseline swabs.

Page 10, Line 14-16

Discussion:

Adequate

Tables:

Adequate

Figures:

NA

Reviewer #2: This article offers some interesting new aspects and shows the impact of skin colonization prior to CVC placement and within 10 days after CVC insertion as risk factor for CA-BSI, but unfortunately, it also includes some questions and annotations which are listed in the following:

2.1.

The aim of the study is defined. In the following further questions (e.g. data of quantitative skin cultures) were investigated without being mentioned in the aim.

The aim of the study as defined in the introduction contains the identification of risk factors for skin colonisation of the CVC insertion site prior to and within 10 days after CVC placement.

Quantitative skin cultures were used to assess skin colonisation.

The wording in introduction and endpoints and microbiology was changed ("skin" was added to baseline and subsequent colonisation for clarification).

Page 3, Line 18-20

Page 6, Line 2-4

2.2.

The methods are appropriate, but two different study centres in two different countries are included with a small sample size. Are they using same standards e.g. skin disinfection (alcohol+/- octenidin) equally?

As mentioned in the introduction, risk factor data were collected within a randomised, controlled trial (reference 12 in the manuscript, Dettenkofer et al. 2010). Within this trial the centres followed standardised protocols for CVC-placement and insertion site care. Assignment of alcohol vs. alcohol + octenidine was randomised (Patients in BS: 32 vs. 33; Patients in FR: 77 vs. 77 in each group, respectively) Data are published (as supporting information table S2) in Dettenkofer et al. 2010 (reference 12 in the manuscript).

"Randomised treatment" is now included into table 1 for the subgroups FR and BS.

Methods were complemented as follows:

Change of dressings and skin antisepsis were performed according to a standard protocol in both centres.

Page 5, Line 2-3

2.3.

CVC insertion was an unstandardized procedure. Patients can not be compared without mentioning risk factors of insertion practice. Information about new risk factors is poor.

As the data are derived from a RCT, study centres were following a standard protocol for CVC insertion. This is described in the Methods section. A standard protocol for insertion can at least exclude some of the major influences on colonisation and infection rates e.g. extent of sterile barrier precautions. We did not aim to identify new risk factors associated with CVC insertion.

Both centres are accredited by joint commission or equivalent (KTQ).

2.4.

In my opinion some important data is missing for the discussion, what about colonisation of catheter-tips without bacteraemia and/ or infection?

Risk factors are interesting, but to my knowledge not too many new information are given to the reader. Of course baseline colonisation can be a risk factor of skin colonisation/ subsequent skin colonisation is a risk factor for tip colonisation.

Data on patients with negative catheter-tip and BSI as well as patients with positive catheter-tip and without BSI were added to results.

Page 12, line 21-24; Page 13, Line 1-2

A paragraph on these data was added to discussion.
Page 15, Line 24; Page 16, Line 1-3

2.5.

Patients undergoing antimicrobial therapy were excluded. How many patients were excluded? Patients with antimicrobial prophylaxis were included. Which prophylaxis was given? Is there the same standard in each study centre? 219 patients were included, during which time period? Are there really so many patients without antimicrobial therapy?

As only the number of eligible patients asked for informed consent was recorded in the underlying RCT we can not provide the number of excluded patients.

Type of prophylactic antibiotics (e.g. quinolone, trimethoprim-sulfamethoxazole) was also not recorded.

Enrollment of patients was realised from 2002-2005 (stated in methods). We may reiterate this figure in results if required.

Based on our previous experience with a pilot study (Dettenkofer et al. Infection 2002, 30:282-285), the recruited patients were usually admitted with newly diagnosed haematologic malignancies for primary therapy or for follow-up therapy. These patients normally didn't have concomitant infections.

2.6.

Limitations of the work are stated, hub colonisation was not evaluated. Other risk factors influenced the study but were not evaluated (e.g. type of dressing, insertion site, CVC type).

Sterile barrier precautions were described as standards in settings and participants, but in the discussion no standard was guaranteed. Why?

As the focus of this study was set on outcome indicators and not process indicators a compliance of 100% could not be guaranteed. For this reason protocols for CVC placement and dressing changes were provided. Adherence was observed whenever possible.

We now added separate analyses for each study centre (see paragraph 2.9.). Therefore we are now able to add analyses with regard to CVC type (tables 3 and 4) and present more detailed data on insertion site and dressing in both study centres (Table 1).

Hub colonisation in haematology patients was evaluated by Tietz et al. (Infect Control Hosp Epidemiol 2005, 26:703-707) but showed to be an unreliable marker in this patient group.

2.7.

Days at risk are not defined.

In our trial days at risk were defined as time period from CVC placement up to two days after catheter removal. In case of patient transfer to another ward/hospital before CVC removal, CA-BSI was observed up to two days after transfer.

The former explanation of days at risk in methods was rephrased for clarification.

Page 7, Line 9 and 12-13

2.8.

Due to the discrepant size of study population at each setting the randomisation of skin disinfectant is not entirely clear.

As described in paragraph 2.2, the two disinfectants were equally distributed within the study centres.

The randomisation procedure is explained in Dettenkofer et al. 2010 (reference 12) as follows:

"Randomization and interventions:

The randomization code was produced by the independent Center for Clinical Studies (FR) using a computerized random-number generator. The study centre was used as a stratification factor and block randomization with randomly varying block length was performed. The randomization was realised using closed envelopes, ensuring that the sequence was concealed before patients entered the trial."

The paragraph on randomisation in methods was rephrased for clarification: "Stratified by centre" was added to "randomly assigned".

Page 4, Line 21

"Further details on study setting and participants have been previously described by Dettenkofer et al. [12]." was added.

Page 5, Line 19-20

2.9.

The influence of the CVC insertion site is known very well. There is a predominantly practice of the subclavian insertion site in the very small Basel cohort. The two study populations are not equal and cannot be compared. Hence, this inhomogeneous study population seems to be a confounder.

Therefore, the objective to identify risk factor for insertion-site cannot be answered.

Another possible confounder seems to be the exclusively use of chlorhexidine silver-sulfadiazine coated CVCs in the Basel cohort. Altogether, a new analyze should be done in each responsible study cohort.

The asymmetric distribution of some factors was not foreseen in the planning phase of the study and is indeed a limitation.

In the revised manuscript we added separate analyses for each study centre with regard to skin colonisation prior to CVC placement and 10 days thereafter.

With regard to the endpoints CVC-tip colonisation and BSI we added separate analyses for study centre FR. Number of patients experiencing these endpoints (3 and 4, respectively) was too small in study centre BS for a separate analysis of study centre BS.

Tables 1-4 and the corresponding passages in methods (Page 8/9, Line 21-2) and results sections (Page 10, Line 9-11; Page 11, Line 13-14; Page 12, Line 7-9 and 14-16) were supplemented.

Discussion was partly rephrased (Page 15, Line 7-15; Page 17, Line 6-8)

2.10.

What conclusions did authors come to?

One aspect is mentioned in the discussion and supports the idea of using routine skin cultures as an option for identifying patients at risk for BSI. Is this a prevention measure?

Perhaps, the use of chlorhexidine-impregnated sponges seems to be an appropriate prevention measure as authors have shown in a RCTs such as Timsit et al. (JAMA 2009;301:1231-41) or Ruschulte et al. (Ann Hematol 2009;88:267-72) e.g. in patients with haematological malignancies.

The important issue of impregnated sponges was included into the discussion (Page 16, Line 21-23; Page 17, Line 1-2, references were supplemented (references 27. Ruschulte et al., and 28. Timsit et al.)

Routine skin cultures by itself are not a preventive measure but could identify patients that would profit from additional preventive measures. Paragraph in discussion was rephrased. Page 17, Line 1-5.

Some minor issues include:

2.11.

P3 line 55: methods are included in the introduction. Skin colonisation is mentioned here but not included in the main questions of the study.

The paragraph resembling methods was removed from the introduction.

The wording in endpoints and microbiology was changed ("skin" was added to baseline and subsequent colonisation for clarification).

Page 6, Line 2-4

2.12.

P9 line 32: Microorganisms are shown in %. In addition, the real number might be reasonable. "CNS are followed by other cocci." Which cocci are included here? Streptococci and S. aureus are mentioned later which confuses the reader.

The real numbers have been added to the manuscript.

The following cocci were recorded separately: S. aureus, CNS, Streptococci, Enterococci.

„Other cocci“ includes all cocci not mentioned above (e.g. Micrococci).

A definition of "other cocci" is now provided within the manuscript.

Page 9, Line 22-23

Signed version will be sent to the Editor-in-Chief

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