ORIGINAL ARTICLE

# Nosocomial infection in small for gestational age newborns with birth weight <1500 g: a multicentre analysis

**Dorothee B Bartels, Frank Schwab, Christine Geffers, Christian F Poets*, Petra Gastmeier***

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See end of article for authors' affiliations

Correspondence to: Dr Dorothee B Bartels, Department of Epidemiology, Public Medicine and Healthcare Systems Research, Hannover Medical School, Carl-Neuberg-Str. 1, OE 5410, 30625 Hannover, Germany; bartels.dorothee@mh-hannover.de

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**Objective:** To investigate whether preterm newborns who are small for gestational age are at increased risk of nosocomial infections and necrotising enterocolitis.

**Design, setting and subjects:** The German national surveillance system for nosocomial infection in very low birthweight infants uses the US Centers for Disease Control and Prevention criteria. 2918 newborns (24–28 weeks), born between 2000 and 2004, were selected after application of predefined inclusion criteria to ensure similar proportions of small and appropriate weight for gestational age newborns across gestational age groups.

**Main outcome measures:** The outcome criterion was at least one episode of nosocomial sepsis, pneumonia or necrotising enterocolitis. Adjusted odds ratios and corresponding 95% CIs were calculated based on general estimating equation models.

**Results:** The study population consisted of 13% (n = 392) small and 87% (n = 2526) appropriate weight for gestational age infants. 33% (n = 950) of the infants experienced at least one episode of sepsis: 42% (n = 163) of small and 31% (n = 787) of appropriate weight for gestational age newborns (adjusted OR 1.41, 95% CI 1.05 to 1.89). Pneumonia was diagnosed in 6% (n = 171) of infants: 8.4% (n = 33) of small and 5.5% (n = 138) of appropriate weight for gestational age newborns (adjusted OR 1.57, 95% CI 1.19 to 5.57). Necrotising enterocolitis was documented in 5.2% (n = 152) of infants: 7.1% (n = 28) of small and 4.9% of (n = 124) appropriate weight for gestational age newborns (adjusted OR 1.20, 95% confidence interval 0.75 to 1.94).

**Conclusions:** Growth-retarded preterm infants seem to be at increased risk of nosocomial infection, irrespective of the responsible pathogen. Future immunological research should elucidate potential causal associations.

Very low birthweight (VLBW, <1500 g) newborns are at increased risk of morbidity and mortality. Besides their immaturity, risk profiles can vary due to a multitude of factors. Growth retardation is one factor conferring additional risk. Recent studies have consistently shown an increased mortality risk for small for gestational age (SGA) infants,[1–3] but results regarding morbidity are conflicting.[4–6]

Nosocomial infection has a large impact on neonatal survival and has important cost implications,[7 8] affecting up to 40% of babies in neonatal intensive care units (NICUs).[9–13] Immunological immaturity (eg, poor phagocytosis or hypogammaglobinaemia), exposure to invasive procedures and prolonged hospitalisation predispose VLBW newborns to nosocomial infection.[7 14 15] However, little is known about nosocomial infection in SGA newborns.[4 11 16–19]

We addressed this issue in a large, multicentre analysis to investigate the association of being SGA and being at increased risk of nosocomial infection—that is, sepsis and pneumonia. In addition, necrotising enterocolitis (NEC) was considered as an outcome criterion.

## METHODS

### Setting and patients

NEO-KISS is a well-established national surveillance system for nosocomial infection in German NICUs. It is based on the US Centers for Disease Control and Prevention (CDC) criteria and has been adapted for this specific age group.[20] The main purpose of NEO-KISS is surveillance of infection, quality assurance and quality improvement. Participating hospitals follow a specifically designed protocol to collect data using standardised forms for all infants with birth weight <1500 g admitted to the NICU.[21] Surveillance ends when the newborn weighs 1800 g or at discharge or death. Currently 47 NICUs are participating in the programme, and data are routinely analysed on a biannual basis. For this study, data were available for 6681 newborns born between 1 January 2000 and 31 December 2004.

We excluded infants with missing data on gestational age, birth weight, sex or multiplicity (n = 333), since these key variables were necessary to define growth status. Small for gestational age was defined as birthweight <10th percentile; appropriate weight for gestational age (AGA) as 10–90% percentile, and large for gestational age (LGA) as >90th percentile, with reference to population-based percentiles, separately for boys and girls and for singletons and twins.[22] Twin percentiles were used for all multiple births. Next we excluded LGA newborns from the comparison group (n = 276) because they may have a different risk profile from AGA infants.

We then introduced gestational age limits to minimise bias due to over-representation of SGA newborns in cohorts defined by birth weight <1500 g.[1 23] The expected proportions of 10% SGA, 80% AGA and 10% LGA were only observed between 24 and 28 weeks. Therefore, 2918 infants with gestational age of 24–28 weeks were included in analyses.

**Abbreviations:** AGA, appropriate for gestational age; CDC, Centers of Disease Control and Prevention; CRIB, Clinical Risk Index for Babies; CPAP, continuous positive airway pressure; CVC, central venous catheter; GEE, general estimating equation; NEC, necrotising enterocolitis; PVC, peripheral venous catheter, SGA, small for gestational age

**Box 1 Definition of nosocomial sepsis**

Onset >72 h after birth and two of the following signs and symptoms:

- Fever (>38°C) or temperature instability (or deregulation of incubator temperature) or hypothermia (<36.5°C)
- Tachycardia (>200/min) or new or increasing bradycardia (<80/min)
- Capillary refill >2 s
- New or increasing apnoea (>20 s)
- Otherwise unexplained metabolic acidosis (BE ⩽10 mmol/l)
- New onset of hyperglycaemia (>7.8 mmol/l)
- Other signs of sepsis (skin colour, biochemical signs (if not already used above as an indication of coagulase-negative staphylococci bloodstream infection), increasing oxygen requirement (intubation), unstable general status, apathy)

AND
(1) Clinical bloodstream infection

- All of the following:
  - Doctor already having instituted treatment for sepsis for at least 5 days
  - Blood culture not done or no organism detected in blood
- No apparent infection at another site

(2) Microbiologically confirmed bloodstream infection

- Recognised pathogen cultured from one or more blood cultures or cerebrospinal fluid and no coagulase-negative staphylococci (pathogen not related to an infection at another site)

OR

- Coagulase-negative staphylococci isolated from at least one blood culture or intravascular line and one of the following:
  - C-reactive protein >20 mg/l
  - Immature:total ratio of neutrophil blood cells >0.2
  - Thrombocytopenia $<100\times10^9$/l
  - Leucocytopenia $<5\times10^9$/l

**Box 2 Definition of nosocomial pneumonia**

Onset >72 h after birth and ONE of the following criteria:

- New or progressive infiltrates
- Consolidation
- Fluid in lobar fissures/pleura

AND
Worsening of gas exchange
AND
FOUR of the following signs and symptoms:

- Temperature instability
- New-onset or increasing bradycardia (<80/min) or new-onset or increasing tachycardia (>200/min)
- New-onset or increasing tachypnoea (>60/min) or apnoea (>20 s)
- New-onset or increasing dyspnoea (retractions, nasal flaring, grunting)
- Increasing production of respiratory secretions and increasing need for suction
- Purulent tracheal secretion
- Isolation of pathogen in respiratory secretions
- C-reactive protein >20 mg/l
- Immature:total ratio of neutrophil blood cells >0.2

### Main outcome measures and variable definitions

We defined nosocomial infection and NEC on the basis of CDC criteria (boxes 1–3).[20]

Nosocomial infection was counted as having occurred at least once or never.[7 10] Endotracheal tube, continuous positive airway pressure (CPAP), peripheral venous catheter (PVC), and central venous catheter (CVC) were also dichotomised (yes/no). Length of stay was the sum of days from birth/admission until reaching a weight of 1800 g, discharge or death. As the assumption of linearity did not hold, we categorised length of stay on the basis of quartiles into 0–33, 34–50, 51–67 and >67 days, and implemented these categories into models as dummy variables. Although gestational age and length of stay are correlated, we kept both because gestational age serves as a surrogate parameter for many underlying pathophysiological characteristics. Gestational age was determined by early ultrasound and recorded as completed weeks. Perinatal centres were defined on the basis of caseload (⩾50 VLBW admissions/year) and local adjacency of delivery unit and NICU.[24] To adjust for hospital volume, we used annual VLBW admissions, dichotomised at the median of all participating units in 2001 (<45 versus ⩾45). Another variable distinguished between university and non-university hospitals. We did not use variables with more than 20% missing values.

**Box 3 Definition of NEC**

Onset >72 h after birth and presence of TWO of the following clinical signs and symptoms without any other recognised reason:

- Vomiting
- Abdominal distention
- Pre-feeding residuals
- Redness of flanks
- Persistent microscopic or gross blood in stools

AND
One of the following criteria:

- Pneumoperitoneum
- Pneumatosis intestinalis
- Unchanging ''rigid'' loops of small bowel

OR
Histological evidence of NEC

**Table 1** Characteristics of the study population (n = 2918) and comparison of small for gestational age (SGA) and appropriate for gestational age (AGA) newborns

| | SGA n (%)* | AGA n (%)* | $\chi^2$ test (p value) |
|---|---|---|---|
| Year of birth | | | |
| 2000 | 40 (10.2) | 319 (12.6) | 0.702 |
| 2001 | 84 (21.4) | 504 (20.0) | |
| 2002 | 79 (20.2) | 483 (19.1) | |
| 2003 | 94 (24.0) | 611 (24.2) | |
| 2004 | 95 (24.2) | 609 (24.1) | |
| Sex | | | |
| Male | 215 (54.9) | 1367 (54.1) | 0.828 |
| Female | 177 (45.2) | 1159 (45.9) | |
| Gestational age (weeks) | | | |
| 24 | 37 ( 9.4) | 343 (13.6) | 0.016 |
| 25 | 55 (14.0) | 441 (17.5) | |
| 26 | 77 (19.6) | 514 (20.3) | |
| 27 | 112 (28.6) | 584 (23.1) | |
| 28 | 111 (28.3) | 644 (25.5) | |
| Median (min, max) birthweight (g) | 595 (300, 850) | 900 (500, 1490) | <0.001† |
| Multiple births | | | |
| No | 310 (79.1) | 1870 (74.0) | 0.034 |
| Yes | 82 (20.9) | 656 (26.0) | |
| Mode of delivery | | | |
| Vaginal | 15 ( 3.8) | 348 (13.8) | <0.005 |
| Caesarean | 372 (94.9) | 2158 (85.4) | |
| MV‡ | 5 ( 1.3) | 20 ( 0.8) | |
| Deceased | | | |
| No | 318 (81.1) | 2254 (89.2) | <0.0005 |
| Yes | 74 (18.9) | 272 (10.8) | |
| Length of stay (days) | | | |
| 0–33 | 99 (25.3) | 638 (25.3) | <0.0005 |
| 34–50 | 34 ( 8.7) | 694 (27.5) | |
| 51–67 | 85 (21.7) | 646 (25.6) | |
| >67 | 167 (42.6) | 532 (21.1) | |
| Sepsis | | | |
| No | 229 (58.4) | 1739 (68.8) | 0.0001 |
| Yes | 163 (41.6) | 787 (31.2) | |
| Pneumonia | | | |
| No | 359 (91.6) | 2388 (94.5) | 0.027 |
| Yes | 33 ( 8.4) | 138 ( 5.5) | |
| Sepsis and/or pneumonia | | | |
| No | 213 (54.3) | 1653 (65.4) | <0.0005 |
| Yes | 179 (45.7) | 873 (34.6) | |
| Necrotising enterocolitis | | | |
| No | 364 (92.9) | 2402 (95.1) | 0.067 |
| Yes | 28 (7.1) | 124 (4.9) | |
| Peripheral venous catheter | | | |
| No | 73 (18.6) | 453 (17.9) | 0.670 |
| Yes | 312 (79.6) | 2057 (81.4) | |
| MV | 7 ( 1.8) | 16 ( 0.6) | |
| Central venous catheter | | | |
| No | 69 (17.6) | 732 (29.0) | <0.0005 |
| Yes | 316 (80.6) | 1778 (70.4) | |
| MV | 7 ( 1.8) | 16 ( 0.6) | |
| Endotracheal tube | | | |
| No | 60 (15.3) | 540 (21.4) | 0.007 |
| Yes | 325 (82.9) | 1970 (78.0) | |
| MV | 7 ( 1.8) | 16 ( 0.6) | |
| Continuous positive airway pressure | | | |
| No | 98 (25.0) | 484 (19.2) | 0.006 |
| Yes | 287 (73.2) | 2026 (80.2) | |
| MV | 7 ( 1.8) | 16 ( 0.6) | |
| Perinatal centre | | | |
| Yes | 327 (83.4) | 2157 (85.4) | 0.321 |
| No | 65 (16.6) | 369 (14.6) | |
| High-volume neonatal intensive care unit | | | |
| Yes | 281 (71.7) | 1939 (76.8) | 0.031 |
| No | 111 (28.3) | 587 (23.2) | |
| University hospital | | | |
| Yes | 182 (46.4) | 1091 (43.2) | 0.229 |
| No | 210 (53.6) | 1435 (56.8) | |

*The percentages have been calculated from the column totals and not the total sample; †Wilcoxon test; ‡missing value.

### Statistical analyses

We conducted univariable analyses based on $\chi^2$, Wilcoxon test and odds ratios (OR) with corresponding 95% confidence intervals. Variables significantly associated with both the exposure (being SGA) and the outcome (nosocomial infection) variable at the $p = 0.25$ level were included in multivariable analyses.[25] However, for face validity reasons we forced gestational age, sex and multiplicity into all multivariable models.

Since newborns from one NICU are not statistically independent due to the same treatment policies, adjusted odds ratios were estimated based on general estimating equation (GEE) models which account for this clustering effect.[26 27] We reduced the significance level in steps = 0.05 each until $p = 0.10$. If this multivariable model building strategy resulted in inclusion of highly correlated variables, such as CVC and PVC, we excluded the variable with lower significance to avoid over-adjustment. Models were considered valid based on the c-statistic, by analysing more complex models and including interaction terms without resulting in significant changes.[25] We used SPSS (version 12.01) and SAS (version 9.1) for all analyses. In Germany, anonymised secondary data research does not require human research committee review.

## RESULTS

Application of exclusion criteria resulted in a study population of 2918 newborns (table 1).

The Clinical Risk Index for Babies (CRIB) score could not be included into further analyses because of 38% missing values. Overall, 38.9% of infants had at least one nosocomial infection or NEC (48.7% SGA, 37.4% AGA). Similar proportions of infants in both groups had more than one episode of sepsis (25.2% SGA, 19.7% AGA; $p = 0.117$) or pneumonia (9.1% SGA, 6.5% AGA; $p = 0.604$). The percentage of nosocomial infections diagnosed only clinically and infections with documented pathogens in the SGA and AGA groups did not differ for either sepsis (documented pathogens in 49.7% and 47.9%, respectively; $p = 0.731$) or pneumonia (documented pathogens in 83.9% and 79.4%, respectively; $p = 0.609$). The types of pathogen responsible also did not differ between the groups (eg, aerobic vs anaerobic vs facultative aerobic-anaerobic; Gram-positive vs Gram-negative bacteria vs fungi vs viruses; data not shown). Table 2 shows the results of the GEE modelling process.

### Sepsis

A third (n = 950, 32.6%) of infants had at least one episode of sepsis: 163 (41.6%) of SGA and 787 (31.2%) of AGA newborns. The crude odds ratio was 1.57 (95% CI 1.27 to 1.96). Besides the forced-in variables we selected mode of delivery, PVC, CVC, endotracheal tube, CPAP, perinatal centre, large NICU and length of stay as potential confounders. The multivariable modelling process resulted in an adjusted odds ratio of 1.41 (95% CI 1.05 to 1.89).

### Pneumonia

Pneumonia was diagnosed in 171 (5.9%) infants: 33 (8.4%) SGA and 138 (5.5%) AGA newborns (crude OR 1.59, 95% CI 1.07 to 2.36). The multivariable modelling process included the forced-in variables and mode of delivery, PVC, CVC, endotracheal tube, CPAP, and length of stay, yielding an adjusted odds ratio of 1.57 (95% CI 1.19 to 5.57).

### Necrotising enterocolitis

In all, 152 (5.2%) newborns developed NEC—28 (7.1%) SGA and 124 (4.9%) AGA (crude OR 1.49, 95% CI 0.98 to 2.28). From the univariable analysis mode of delivery, PVC, CVC, endotracheal tube, perinatal centre, large NICU, and length of stay

**Table 2** Crude and adjusted odds ratios (OR) with corresponding 95% confidence intervals, results of the general estimating equation (GEE) models

| Variables adjusted for | Sepsis | | Pneumonia | | NEC | |
|---|---|---|---|---|---|---|
| Crude OR (95% CI) | 1.57 | (1.27 to 1.96) | 1.59 | (1.07 to 2.36) | 1.49 | (0.98 to 2.28) |
| Adjusted OR (95% CI) | 1.41 | (1.05 to 1.89) | 1.57 | (1.19 to 5.57) | 1.20 | (0.75 to 1.94) |
| Male | 1.16 | (1.00 to 1.33) | 0.95 | (0.69 to 1.30) | 0.94 | (0.92 to 1.83) |
| Gestational age (weeks) | | | | | | |
| 24 | 1.85 | (1.45 to 2.35) | 2.57 | (1.19 to 5.57) | 1.55 | (0.59 to 4.06) |
| 25 | 2.01 | (1.46 to 2.77) | 2.20 | (1.23 to 3.95) | 1.02 | (0.48 to 2.19) |
| 26 | 1.83 | (1.44 to 2.31) | 1.88 | (1.07 to 3.23) | 1.04 | (0.51 to 2.13) |
| 27 | 1.35 | (1.04 to 1.76) | 1.46 | (0.88 to 2.44) | 1.14 | (0.68 to 1.91) |
| 28 | Reference | | | | Reference | |
| Multiple birth | 1.07 | (0.89 to 1.29) | 0.78 | (0.54 to 1.12) | 1.11 | (0.78 to 1.58) |
| Mode of delivery | * | | 0.62 | (0.39 to 0.98) | | |
| Peripheral catheter | 2.27 | (1.70 to 3.04) | 2.06 | (1.23 to 3.45) | | |
| Central venous catheter | | | | | 3.13 | (2.06 to 4.75) |
| Endotracheal tube | 1.82 | (1.54 to 2.17) | 5.46 | (2.46 to 12.12) | 3.43 | (1.82 to 6.47) |
| High-volume NICU | | | | | 3.14 | (1.99 to 5.17) |
| Length of stay (days) | | | | | | |
| 0–33 | Reference | | Reference | | Reference | |
| 24–0 | 2.03 | (1.42 to 2.90) | 2.07 | (1.08 to 3.96) | 0.97 | (0.65 to 1.45) |
| 51–67 | 2.83 | (2.02 to 3.97) | 3.60 | (1.96 to 6.63) | 0.70 | (0.50 to 0.99) |
| >67 | 5.74 | (4.08 to 8.07) | 4.71 | (1.6 to 6.63) | 1.60 | (1.01 to 2.52) |

*The empty fields are due to variables losing significance during the modelling process.

were selected. The modelling process led to an adjusted odds ratio of 1.20 (95% CI 0.75 to 1.94).

## DISCUSSION

This large multicentre analysis suggests that VLBW infants who are small for gestational age are at increased risk of nosocomial infection. To our knowledge this is the largest study of nosocomial infection in preterm growth-retarded infants, including variables such as length of hospital stay and device application. Overall 36% of infants had at least one nosocomial sepsis or pneumonia. Others have reported 19.6% for infants ⩾24 weeks,[11] and 14.4% for all newborns admitted to NICU.[9] The proportion of infants developing nosocomial infection was larger in this study probably due to the extreme prematurity and fairly narrow gestational age limits of our study population.

Bloodstream infection is the most common nosocomial infection in the NICU setting.[28] Case fatality rates range from 2% to 50%.[29] Overall in the present study, 33% of infants had at least one sepsis. This proportion is similar to those reported in some,[10 30] but not all other studies in this field.[14 31 32] We found a 41% increased risk of sepsis for SGA infants. VLBW infants were at increased risk for nosocomial infection, even after adjusting for length of NICU stay.[33] The most important risk factors for nosocomial infection in this study were gestational age (adjusted ORs 1.35–2.01) and length of stay (adjusted ORs 2.03–5.74). Both were highly correlated, but length of stay seemed to increase the risk even more than gestational age and showed a dose–response-like relationship to the risk of sepsis.

Our results with regard to pneumonia have to be interpreted with caution because of the small numbers. Chandra stated that upper and lower respiratory tract infections are three times more frequent in SGA than AGA infants but did not offer any details or pathophysiological explanations.[34] Moreover, the diagnosis may not always be valid due to imprecise diagnostic criteria and misclassification in favour of sepsis.[7 13 35 36] Therefore we additionally analysed having developed sepsis *or* pneumonia. The adjusted odds ratio of 1.41 (95% CI 1.09 to 1.84) confirmed our results for sepsis.

Sepsis and NEC are the most common infections in VLBW infants.[33] Moreover, NEC is the most frequent surgical emergency.[37] Immaturity, ischaemia, enteral feeding, damaged intestinal mucosa and pathogenic organisms are major risk factors.[12 38] Although NEC is not regarded as a nosocomial infection, it is included in the surveillance system because of its potentially clustered incidence.[39] The overall occurrence of 5% in the present study is lower than that reported by others.[40] We observed a slightly increased adjusted odds ratio of 1.20 (95% CI 0.75 to 1.94) for SGA newborns. Some authors have reported an increased incidence of NEC in growth-retarded infants,[6 41] with suspicion of end-organ damage in utero.[41] However, our results may be not be reliable owing to our small numbers, and further studies are required to investigate whether and how growth retardation increases susceptibility to NEC.

A striking finding was the increased adjusted odds ratio for NEC in high-volume hospitals (adjusted OR 3.14, 95% CI 1.99 to 5.17). This may be due to larger NICUs preferentially being linked to departments of paediatric surgery; severely ill newborns will be transferred to these large perinatal centres.[12]

We included relatively little information on maternal, pregnancy and perinatal variables. However, we do not consider this a major limitation since these variables may be less meaningful when analysing nosocomial (late-onset) infections. Insufficient casemix adjustment due to missing values in the CRIB score variable may have biased the results. However, we incorporated information on length of stay and device use, which are important potential confounders and have rarely been adjusted for in other studies. This information is particularly important for interpreting results based on the assumption of equal exposure probability. Documentation of device-associated infections was rather non-specific, eg a ''device-associated infection'' was not linked to a specific infection if more than one infection occurred. There were similar proportions of SGA and AGA newborns with ''device-associated infections'' ($p = 0.133$).

What is the biological plausibility of our finding? The present study was not designed to investigate mechanisms. Hence we cannot explain the apparent association between nosocomial infection and SGA status. Although previously reported in a study from India,[17] the association may be spurious. Early studies, however, suggested possible interactions between immunological function and nutritional status, or decreased T-lymphocyte numbers in SGA newborns, and a more pronounced hypogammaglobulinaemia compared with AGA infants.[42 43] Thymic atrophy and prolonged impairment of cell-mediated immunity (eg, reduced lymphocyte numbers and deranged CD4:CD8 ratios) have been found in SGA infants and animal models of intrauterine growth retardation.[18 34]

## What is already known on this topic

- Preterm infants are at increased risk of infectious diseases due to the immaturity of their immune system and prolonged hospital stay.
- Nosocomial infections are a considerable burden in healthcare, in particular, in neonatal intensive care units.

## What this study adds

- There is an increased risk of nosocomial infection among preterm small for gestational age (SGA) infants, and growth retardation is an additional risk factor besides immaturity.
- The risk of sepsis is 40% higher in preterm SGA infants, even after adjustment for length of hospital stay.
- The risk of necrotising enterocolitis in very low birthweight infants who are small for gestational age is increased by 20%.

In summary, preterm SGA infants seem to be at increased risk of nosocomial infection, but this is not related to a specific group of pathogens and is independent of the duration of hospital stay. Our findings should alert clinicians to this additional risk in preterm SGA infants and reinforce the focus on immunological research in growth-retarded newborns. Since there is an increased risk of mortality among SGA newborns[1] and sepsis has a major impact on survival in NICU,[44] this association should be investigated in more detail.


### Authors' affiliations

**Dorothee B Bartels,** Department of Epidemiology, Public Medicine and Healthcare Systems Research, Hannover Medical School, Hannover, Germany
**Frank Schwab, Christine Geffers, Petra Gastmeier,** Institute of Hygiene, Charité-University Medicine in Berlin, Berlin, Germany
**Christian F Poets,** Department of Neonatology, University Children's Hospital, Tübingen, Germany


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*C F Poets and P Gastmeier have contributed equally to this study.

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