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Time-dependent analysis of length of stay and mortality due to urinary tract infections in ten developing countries: INICC findings

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Summary *Objectives:* To estimate the excess length of stay (LOS) and mortality in an intensive care unit (ICU) due to a Catheter associated urinary tract infections (CAUTI), using a statistical model that accounts for the timing of infection in 29 ICUs from 10 countries: Argentina, Brazil, Colombia, Greece, India, Lebanon, Mexico, Morocco, Peru, and Turkey.
Methods: To estimate the extra LOS due to infection in a cohort of 69,248 admissions followed for 371,452 days in 29 ICUs, we used a multi-state model, including specific censoring to ensure that we estimate the independent effect of urinary tract infection, and not the combined effects of

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[l] Refer Appendix section for International Infection Control Consortium, listed by country alphabetically.

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Mortality;
Developing countries;
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multiple infections. We estimated the extra length of stay and increased risk of death independently in each country, and then combined the results using a random effects meta-analysis.
Results: A CAUTI prolonged length of ICU stay by an average of 1.59 days (95% CI: 0.58, 2.59 days), and increased the risk of death by 15% (95% CI: 3, 28%).
Conclusions: A CAUTI leads to a small increased LOS in ICU. The increased risk of death due to CAUTI may be due to confounding with patient morbidity.

Introduction

Catheter associated urinary tract infections (CAUTI) are a worldwide problem that may lead to increased patient morbidity, cost and mortality.[1–3] The literature is divided on whether there are real effects from CAUTI on length of stay or mortality. Platt[4] found the costs and mortality risks to be large yet Graves et al found the opposite.[5] A review of the published estimates of the extra length of stay showed results between zero and 30 days.[6] The differences in estimates may have been caused by the different epidemiological methods applied. Accurately estimating the effects of CAUTI is difficult because it is a time-dependent exposure. This means that standard statistical techniques, such as matched case-control studies, tend to overestimate the increased hospital stay and mortality risk due to infection. The aim of the study was to estimate excess length of stay and mortality in an intensive care unit (ICU) due to a CAUTI, using a statistical model that accounts for the timing of infection. Data collected from ICU units in lower and middle income countries were used for this analysis.[7,8] There has been little research for these settings, hence the need for this paper.

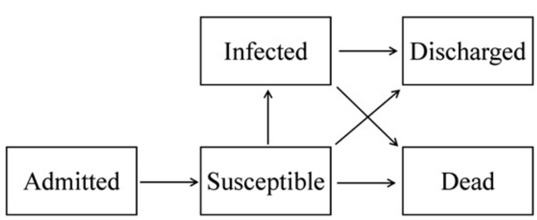

Figure 1 Multi-state model used to estimate the time-dependent effect of nosocomial infection on length of stay and risk of death.

Methods

We aimed to estimate the impact of infection on both length of stay and risk of death. Infection is a time-dependent variable, and so it is essential to use statistical methods that correctly account for this, otherwise estimated effects can be severely biased.[9,10] Therefore to estimate the extra length of stay due to infection we used the methods described in Allignol et al,[11] and to estimate the risk of mortality due to infection we used the methods described in Wolkewitz et al.[12]

Both methods arrange the data according to the multi-state format shown in Fig. 1. A patient enters the ICU and becomes susceptible to infection after having a urinary catheter. If the time to catheter is not modelled then the estimated effects of infection are prone to the "length bias".[13] Once a patient has had a urinary catheter they may either be discharged or die, or they may first become infected. If the time to infection is not modelled then this leads to the time-dependent bias.[9]

We censored patients when it was not known whether they died or were discharged, using a censoring date of their last day in ICU. We also censored patients who contracted another unrelated infection (e.g., an unrelated blood stream infection) using the date of the unrelated infection. This censoring is used to ensure that we estimate the independent effect of urinary tract infection, and not the combined effects of multiple infections.

We estimated the extra length of stay and increased risk of death independently in each country. We then combined the results using a random effects meta-analysis. As a sensitivity analysis we re-ran the meta-analysis leaving out each country in turn. This analysis assesses whether there is a particular country that has a strong influence on the estimated overall effect. As another sensitivity analysis we first stratified the admissions according to the Average Severity Illness Score

Table 1 Sample characteristics by country. All statistics for admissions with a urinary catheter, except the Admissions column.

Country	Admissions	Admissions with a catheter (%)	Length of stay, days	Mean age, years	Men (%)	Dead (%)
Argentina	17,910	10,528 (59)	79,788	71	5231 (29)	2634 (15)
Brazil	2452	1904 (78)	24,074	56	1054 (43)	520 (21)
Colombia	8155	5480 (67)	44,354	50	2923 (36)	1076 (13)
Greece	105	87 (83)	912	66	56 (53)	22 (21)
India	24,583	17,930 (73)	106,981	55	12,669 (52)	1951 (8)
Lebanon	383	378 (99)	3386	62	266 (69)	81 (21)
Mexico	3423	2187 (64)	15,974	41	919 (27)	359 (10)
Morocco	2584	1435 (56)	12,046	45	740 (29)	660 (26)
Peru	1970	1506 (76)	9497	53	811 (41)	283 (14)
Turkey	7683	5729 (75)	74,440	50	3474 (45)	1909 (25)
Total	69,248	47,164 (68)	371,452	57	28,143 (41)	9495 (14)

Table 2 Estimated extra length of stay (LoS) and relative risk of death due to a nosocomial urinary tract infection. Cells show the mean and 95% confidence interval in parenthesis.

Country	Total extra LoS, days	Relative risk of death
Argentina	0.90 (0.15, 1.66)	1.26 (1.08, 1.48)
Brazil	0.95 (−2.71, 4.61)	0.97 (0.60, 1.59)
Colombia	2.43 (−0.03, 4.89)	0.75 (0.47, 1.17)
Greece	0.94 (−5.93, 7.81)	1.29 (0.35, 4.70)
India	2.41 (0.24, 4.58)	1.06 (0.67, 1.67)
Lebanon	−0.83 (−3.83, 2.17)	1.40 (0.56, 3.46)
Mexico	2.46 (0.49, 4.43)	1.07 (0.66, 1.73)
Morocco	1.39 (−0.28, 3.05)	1.19 (0.79, 1.81)
Peru	−0.33 (−2.08, 1.42)	0.77 (0.36, 1.64)
Turkey	5.88 (3.18, 8.58)	1.13 (0.90, 1.43)
Meta-analysis	1.59 (0.58, 2.59)	1.15 (1.03, 1.28)
Heterogeneity test	1.3 (p-value = 0.015)	0.0 (p-value = 0.66)
Leave-one-out meta-analysis, mean (country)		
Smallest	1.11 (Turkey)	1.05 (Argentina)
Largest	1.86 (Peru)	1.18 (Colombia)

(ASIS) score. We estimated the extra length of stay and risk of death for admissions in the lower three ASIS categories ("healthier" group), and in the upper two categories ("sicker" group). ASIS was not collected in Greece or Lebanon, so they were excluded from this sensitivity analysis.

For all analyses the R 2.4.1 software was used (R Foundation, Vienna, Austria), using the 'etm' library to estimate the extra length of stay due to infection, and the 'rmeta' library for meta-analysis.

Results

Table 1 shows the summary statistics by country. Across all ten countries there were 371,452 ICU days observed after the patient had a urinary catheter. On average 14% of admissions ended in death.

Table 2 shows the estimated extra LoS and risk of death due to infection by country and the meta-analysis summary. On average a UTI infection led to 1.59 extra days in the ICU

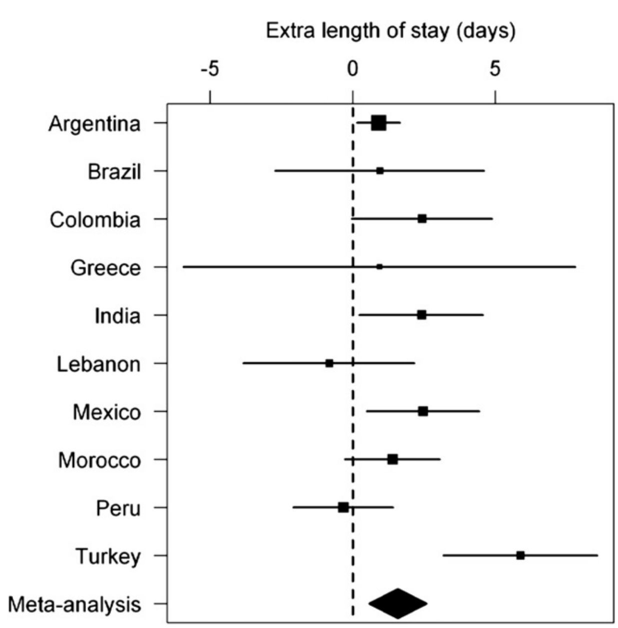

Figure 2 Extra length of stay in days due to a nosocomial urinary tract infection in each country and the overall extra length of stay from a meta-analysis. The squares are the mean estimates and the horizontal lines the 95% confidence intervals. The squares are inversely proportional to the standard error of the estimate.

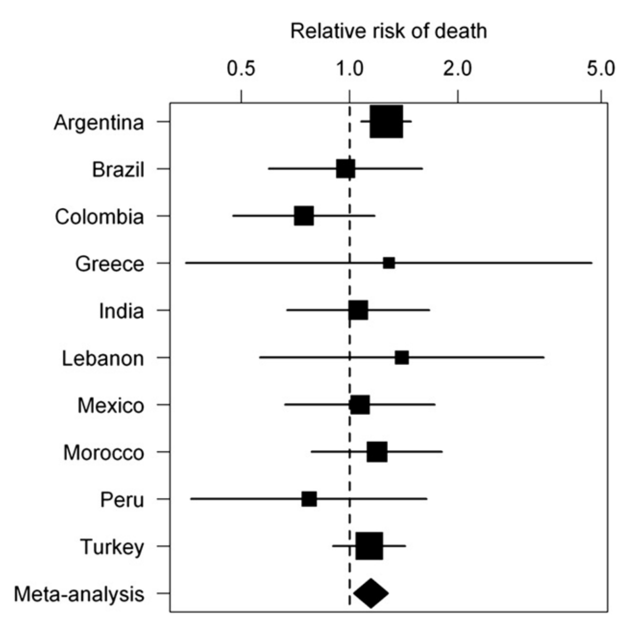

Figure 3 Relative risk of death due to a nosocomial urinary tract infection in each country and the overall relative risk from a meta-analysis. The relative risk axis is on a log scale. The squares are the mean estimates and the horizontal lines the 95% confidence intervals. The size of the squares is inversely proportional to the standard error of the estimate.

(95% CI: 0.58, 2.59 days) and a 15% increase in the risk of death (95% CI: 3, 28%).

Fig. 2 plots the mean extra length of stay in each country and the meta-analysis. The extra length of stay was far longer in Turkey (mean = 5.88 days). The result from Turkey is the main driver of the statistically significant heterogeneity in the extra LoS between countries (p-value = 0.015). Without Turkey the overall extra LoS drops from an average of 1.59 days to 1.11 days.

Fig. 3 plots the mean relative risk of death in each country and the meta-analysis. There was more consistency across countries in the relative risk of death compared with the extra LoS. The most unusual result was from Colombia, where an infection reduced the relative risk to 0.75, although this reduction was not statistically significant (95% CI for RR: 0.47, 1.17). Without Colombia the overall relative risk of death rose slightly from 1.15 to 1.18.

Table 3 shows the results after stratifying on ASIS. The relative risk of death remained high in the "healthier" ASIS group (mean RR = 1.16), but the increase was now not statistically significant. This lack of statistical significance could be due to a drop in sample size, rather than a change in the mean. In the "sicker" ASIS group the mean relative risk of death was much closer to one, and the increased risk was no longer statistically significant. The estimated extra lengths of stay were similar to the unstratified estimate for both ASIS groups.

Conclusions

We used the best available statistical methods to estimate the extra length of stay and risk of death due to nosocomial urinary tract infection. These methods treat both the timing of the catheter and the timing of infection as time-dependent variables (Fig. 1). This means the results are not prone to the length bias (which would underestimate the risks of infection), or the time-dependent bias (which would overestimate the risks of infection).

The results were quite consistent between countries and showed a modest increase in the extra length of stay due to infection as, on average, there were 1.59 extra days. This increase was strongly statistically significant, and had a similar mean after stratifying on ASIS score. A relatively small increase in hospital stay still represents an important and potentially costly consequence of infection.

The relative risk for mortality was 1.15 on average, and again this increase was strongly statistically significant. However, this strong effect disappeared after stratifying on ASIS score. This suggests that the original increased risk was due to confounding by ASIS. We know that sicker patients have an increased risk of death, the confounding would be complete if sicker patients were also more likely to get urinary tract infections. Clec'h et al had similar findings as they found a statistically significant increased risk of death for patients with a UTI that disappeared after matching and adjustment.[14]

The method we used to estimate the extra LoS and risk of death due to infection is not able to adjust for important covariates such as age. However, a recent study by Beyersmann et al demonstrated that adjusting for the timing of infection is likely to be more important than adjusting for confounders, as they found that adjusting for 20 potential confounders did not redeem the time-dependent bias.[15]

Intensive care units of developing countries should improve the implementation of evidence based strategies in order to prevent catheter associated urinary tract infections, because they are associated with extra length of stay and mortality.

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Appendix. International Infection Control Consortium, listed by country alphabetically

Argentina: Sandra Guzman (Centro Médico Bernal, Buenos Aires); Luis Pedro Flynn, Diego Rausch, Alejandro Spagnolo (Sanatorio Británico, Rosario); Guillermo Benchetrit, Claudio Bonaventura, María de los Ángeles Caridi, Adriana Messina, Beatriz Ricci (Centro Gallego de Buenos Aires, Buenos Aires); María Laura Frías, Griselda Churruarín (Clínica Modelo de Lanús, Lanús); Daniel Sztokhamer (Clínica

Table 3 Estimated extra length of stay (LoS) and relative risk of death due to a nosocomial urinary tract infection stratified by Average Severity Illness Score (ASIS). The higher the ASIS score the sicker the patient.

ASIS (categories)	Admissions	Total extra LoS, days	Relative risk of death
"Healthier" (1–3)	22,148	1.44 (−0.24, 3.12)	1.16 (0.96, 1.40)
"Sicker" (4–5)	15,150	1.73 (0.64, 2.83)	1.04 (0.88, 1.23)
Total	37,298		

Estrada, Buenos Aires); Luisa C. Soroka (Hospital Interzonal General de Agudos Evita, Lanús); Silvia Forciniti, Marta Blasco, Carmen B. Lezcano (Hospital Interzonal General de Agudos Pedro Fiorito, Avellaneda); Carlos Esteban Lastra (Hospital Narciso López, Lanús); Mónica Viegas, Beatriz Marta Alicia Di Núbila, Diana Lanzetta, Leonardo J. Fernández, María Adelaida Rossetti, Adriana Romani, Claudia Migazzi, Clarisa Barolin, Estela Martínez (Hospital Interzonal General de Agudos Presidente Perón, Avellaneda) Alicia Kobylarz (Hospital Materno Infantil Eduardo Oller Solano).

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