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High absolute risk of severe infections among Indigenous adults in rural northern Australia is amplified by diabetes – A 7 year follow up study

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ABSTRACT

Aims: To quantify the risk of hospitalization for infections in Indigenous Australian adults with diabetes in rural and remote communities.
Methods: 2787 Indigenous adults including 396 with diabetes at baseline from 19 communities in North Queensland from 1998 to 2007 were included in the study. Main measures were weight, height, waist circumference, blood pressure, fasting glucose, lipids, self-reported tobacco smoking, alcohol intake and physical activity. Baseline data were linked to hospital separation data using probabilistic linkage. The association between diabetes and hospitalization for all causes and infections was investigated using generalized linear model (GLM) and adjusted for other baseline measurements.
Results: During a median follow up of 7 years, 461 participants were hospitalized with 762 episodes of infection. 277 patients with diabetes (70%) were hospitalized at least once. 40% (110 in 277) were for community acquired infections. Patients with diabetes were twice as likely to be hospitalized for infections as those without diabetes (adjusted risk ratio 2.1, 95% CI 1.6–2.8), especially for urinary tract infections, cellulitis, and septicaemia. Median length of stay was 6 (IQR 3–13) days for diabetes patients compared to 3.4 days (IQR 2–6.4) for those without diabetes ($P < 0.001$)
Conclusions: In addition to an already high rate of hospitalizations for infections among Indigenous compared to non-Indigenous Australians, diabetes confers an additional risk for severe infections especially urinary tract infection, cellulitis and septicaemia. Recovery is also comparatively slower. Early recognition and management of these infections in the primary care setting may reduce this risk and better control of glycaemia and its risk factors may improve underlying immune dysfunction.

1. Introduction

Diabetes has become widely prevalent and is associated with increased risk of cardio metabolic complications and infections including increased infection-related mortality (Magliano et al., 2015; Nwaneri, Cooper, & Bowen-Jones, 2013). Common excess diabetes-related infections include respiratory tract infections, pyelonephritis and cystitis, urinary tract infections, soft-tissue infections, ear infections and cholecystitis (Joshi, Caputo, Weitekamp, & Karchmer, 1999; Nitzan, Elias, Chazan, & Saliba, 2015). This doubling of infection risk appears to be consistent across different studies and also reflects the pattern of community-acquired infection in the general population (Casqueiro, Casqueiro, & Alves, 2012; Klekotaka, Mizgala, & Krol, 2015). The raised risk among people with diabetes suggests a general underlying impairment in immune function which includes lowered interleukin production in response to specific infections, neutrophil dysfunction, the direct effect of glycaemia which may increase virulence of some pathogens, and the combined effect of glycosuria and urinary tract dysmotility (Peleg, Weerarathna, McCarthy, & Davis, 2007).

Indigenous Australians have extremely high prevalence of type 2 diabetes with higher proportions in remote Indigenous communities where up to 50% of adults are affected (Australian Indigenous Australian Indigenous HealthInfoNet, 2015). Likewise, the incidence of diabetes is around 8 times higher than the non-Indigenous population (McDermott, Li, & Campbell, 2010). Indigenous Australians are hospitalized at nearly 4 times the rate for the general population for all causes (Australian Institute of Health & Welfare, 2011). The risk of infections in Indigenous Australians with diabetes has been reported first time in Central Australia of a double the risk compared to matched Aboriginal controls (Patel, Phillips, & Cabaron, 1991). The other urban Western Australian study in a sample of 120 adults found a similar within-Aboriginal comparison risk (Hamilton et al., 2013). Reports from Canada, the Netherlands and non-Aboriginal Australia suggest increased susceptibility to pneumonia, urinary tract

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infections, septicaemia and cellulitis (Hamilton et al., 2013; Muller et al., 2005; Shah & Hux, 2003).

Here we quantify the 7 year risk of hospitalization for infectious diseases including respiratory/ear, nose, and throat (ENT), urinary, digestive, cellulitis, septicaemia, and the length of hospital stay (LOS) in a large cohort of Aboriginal and Torres Strait Islander adults with and without diabetes from rural and remote communities in North Queensland between 1998 and 2007.

2. Methods

2.1. Study population

Baseline data were collected from 2787 adults in 19 rural Indigenous communities across three health districts in far north Queensland. The cohort participated in the "Well Person's Health Check" (WPHC) between 1998 and 2000. Methods for this cross sectional study have been reported in detail elsewhere (Miller et al., 2002). Briefly, all Indigenous residents of the communities were invited to attend a health check. The study achieved a participation rate of 44.5% with greater participation noted in smaller communities based on the local census data. The study protocols were approved by the Cairns Base Hospital Human Research Ethics Committee with support from the peak Indigenous Health Organizations, Apunipima Cape York Health Council and the Torres Strait and Northern Peninsula Area Health Council.

2.2. Measurements

Weight was recorded with light clothing to the nearest 0.1 Kg, and height and waist circumference (WC) were recorded to the nearest centimetre by technicians. Physical activity was self-reported using a 7-day recall method and was defined using the WHO criteria in which 'enough' means doing moderate to vigorous physical activity for more than 30 min/d for 5 days in the week before the survey. Daily consumption of tobacco and alcohol were self-reported. Blood pressure (BP) was the average of three measurements using a Dinamap model 800 automated blood pressure monitor (Critikon; Tampa FL, US). Baseline hypertension was ascertained either by detection of high BP at examination (measured BP >140/90 mmHg) or previous confirmed diagnosis or currently prescribed antihypertensive medication (by medical record review).

Total cholesterol, high density lipoprotein cholesterol (HDLC), triglycerides, and glucose were measured on fasting blood using photometric enzyme endpoint assay with Cobas Integra 700/400 (Roche Diagnostic, USA). Diabetes was defined as either clinical diagnosis verified by the participants' medical records or a 2 hour glucose tolerance test, or fasting blood glucose level >7.0 mmol/L.

2.3. Hospitalization for infections

Hospitalization for consenting WPHC participants during 1998–2007 was identified via a manual search (by a registered nurse with experience working in the region) of the Queensland Health hospital record systems. Hospitalization data were merged with baseline survey data by probabilistic linkage using a mapping table, which linked WPHC reference number, hospital facility code and local unit record number.

Hospitalized infections were grouped into the following: respiratory/ENT, digestive, urinary, cellulitis, and septicaemia. Respiratory/ENT infections included bronchitis, pneumonia and others, and ENT infections; digestive infections included gastroenteritis, hepatitis, cholecystitis, and appendicitis; urinary infections included pyelonephritis and other urinary tract infections, pelvic inflammatory diseases. All hospital admissions with the International Classification of Disease (ICD)-9-CM and ICD-10-AM codes for the selected infections as principal diagnosis were identified. Table 1 listed the ICD codes for the selected infections from hospitalization separation during 1998–2007. The LOS of each corresponding admission was recorded and the mean LOS was summarized within each infection groups. Incidence was defined as any hospitalized infections after the enrolment date.

2.4. Statistical analysis

Baseline characteristics including age, sex, and ethnicity, self-reported behaviours including smoking, and drinking, blood pressure, diabetes/fasting glucose, blood lipids, were compared between hospitalizations and by infections and tested using t test or chi-square test or Mann–Whitney U-test or Fisher's exact test. The risk of hospitalized infections with baseline diabetes or glucose tertiles was investigated using generalized linear model (GLM). The outcome was hospitalized infections, and the study factor was baseline diabetes/glucose tertiles. The family in the models was "binomial" and the link was "log". The association was further adjusted for age, sex, body mass index (BMI), other biomedical factors (blood pressure, lipid), and lifestyle factors (smoking, drinking, physical activity). LOS in days by baseline diabetes was compared and tested using Mann–Whitney U test. The association with diabetes was assessed using log transformed LOS as outcome in GLM with family "gauss" and link "identity" and adjusted for the above factors. The analysis was carried out using STATA 13 (STATACorp, College Station, TX, USA) and significance level was set at two-sided $P < 0.05$.

3. Results

3.1. Characteristics of the study cohort and hospitalization for infections

Among the 2787 Indigenous participants included in this study, 1448 were males (52.0%) with an overall mean age of 37.1 (SD 15.3 years). 1641 were Aboriginal people. At baseline, 61% were overweight and/obese defined as BMI ≥25 kg/m^2, 58% self-reported as smokers and 69% as **alcohol** drinkers, less than a quarter (24%) of people met the PA recommendations. 396 people (14%) had diabetes and 790 (28%) had hypertension. A total of 1753 were hospitalized during 1998–2007. 277 diabetes patients in the 396 participants (70%) were admitted at least once during the study period. Baseline characteristics were not significantly different by hospitalization (Appendix Table A1).

During the follow up, a total of 762 episodes of infections were identified in 461 participants from the cohort. 182 participants were hospitalized with infections of respiratory system and ENT, 73 with infections of the digestive system, 107 had infections of the urinary system, 168 with cellulitis, and 34 with septicaemia (Table 2). 110 inpatients were with infections in the 227 diabetes patients (40%).

Table 1
International Classification of Disease (ICD)-9-CM and ICD-10-AM codes for selected infections in the present study.

Infection	ICD-9-CM	ICD-10-AM
Respiratory/ENT	380, 382, 461–463, 465, 466, 472, 480–488, 490–493, 519	A161, A169, J10–J18, J20–J21, J00–06, J31–J32, J40, J45, H66–H67, J85
Digestive	001–009, 70	A00–A09, B15–B19, K35, K37, K80–K81
Urinary	540, 575, 590, 595, 599, 601, 090–099	N10–13, N30, N39, N41, R30, R33. A50–A54, A70–A74
Cellulitis	680–686, 785, 917	L00–L04, L08, L88–L98, R02
Septicaemia	036, 038, 041, 790, 995	A39–41, A49

Table 2
New hospitalization for selected infections from 1998 to 2007 for the whole WPHC cohort.

	Infections	No	Episodes	LOS median (IQR)
Respiratory/ENT	Pneumonia and others	132	176	4 (2–7)
	Bronchitis	37	68	3 (1–5)
	ENT infection	31	33	2 (1–4)
Digestive	Gastroenteritis	4	4	2 (1.5–2)
	Hepatitis	1	1	5
	Cholecystitis	42	48	2.5 (1–4.5)
	Appendicitis	28	30	3.5 (2–6)
Urinary	PID	36	43	3 (1–6)
	Pyelonephritis and UTI	72	102	2 (4–3)
Cellulitis	Cellulitis	168	216	4 (2–7)
Septicaemia	Septicaemia	34	41	8 (5–13)

3.2. Biomedical factors including baseline diabetes and hospitalization for infections

Table 3 summarizes the baseline characteristics of the patients hospitalized with infections. Hospitalization with respiratory/ENT infections was more likely among older participants or with lower BMI and higher BP. Hospital admission for gastro-intestinal infections was more likely among females and those with lower SBP and smokers, but was not different by age, ethnicity, and BMI, lipids and drinking profile. Hospitalization with infections of the urinary system was more likely for females, those with lower cholesterol and HDLC, and smokers, but did not differ by age, ethnicity, BMI and drinking status. Admission with cellulitis was more likely among older participants, or with higher BMI or SBP. Hospitalization with septicaemia was more likely among older participants, with higher BMI or BP, or non-smokers.

The proportion of patients with severe infection was significantly higher in those with diabetes at baseline (396 patients) except for infections of the digestive system. For example, 9.3% participants with diabetes were hospitalized with respiratory/ENT infections compared to 6.5% without diabetes during the follow up period ($P < 0.014$) (Table 4).

Among the 396 participants with diabetes at baseline, 383 had a fasting glucose in the 3rd tertile (≥5.3 mmol/L). 7 were in the other tertiles and 6 patients did not have baseline glucose recorded. Among those free of diabetes at baseline, increased glucose was not associated with infection hospitalization. The proportion of total infections was higher in those with glucose ≥5.3 (20.7% for the 3rd glucose tertile vs 15% for the 1st tertile, $P < 0.001$), particularly for cellulitis and septicaemia (Appendix Table A2).

Table 4
Number (%) of people hospitalized with selected infections by baseline diabetes.

	No diabetes $n = 2391$	Diabetes Yes $n = 396$	p
Respiratory/ENT	145 (6.1)	37 (9.3)	0.014
Digestive	63 (2.6)	10 (2.5)	0.899
Urinary	74 (3.1)	33 (8.3)	<0.001
Cellulitis	111 (4.6)	57 (14.4)	<0.001
Septicaemia	17 (0.7)	17 (4.3)	<0.001
Overall	348 (14.5)	113 (28.5)	<0.001

P from chi-square test.

3.3. The association between diabetes/glucose and hospitalization for infections

Regression models showed that participants with diabetes at baseline were twice as likely to be hospitalized for any infection as those without diabetes (adjusted risk ratio 2.1, 95% CI: 1.6–2.8). Specifically, compared to those free of diabetes, urinary infection conferred the greatest excess risk (adjusted RR 3.6, 95% CI: 2.2–5.7), followed by septicaemia and cellulitis (adjusted RR = 3.3 (95% CI 1.6–6.8 and 2.9, 95% CI: 2.0–4.1), respectively. Baseline fasting glucose ≥5.3 mmol/L conferred a crude overall excess risk of infection of 1.4 but this reduced after adjustment. However for urinary infections, the risk excess remained after adjustment, suggesting that glycaemia itself may play a role in these specific infections (Table 5).

Median LOS for all infections was greater in older and Aboriginal participants but not related to BMI, blood pressure, blood lipids or lifestyle factors. The LOS for infections of respiratory/ENT, digestive, urinary systems as well as cellulitis varied from 4 to 5 days and was longer in diabetes patients than those without (LOS varied from 2.5 to 3.5 days) (Table 6). Log transformed total LOS for all infections in diabetes patients was 1.6 times (95% CI 1.3–2.0) greater than those without diabetes after adjustment, and log LOS for urinary infections was doubled in diabetes (95% CI 1.2–3.3).

4. Discussion

An extremely high background rate of community-acquired infection plus high prevalence of type 2 diabetes among Indigenous Australians leads to excess hospitalization for infections. We found on

Table 3
Characteristics of hospitalized participants by selected infections in North Queensland.

	Respiratory/ENT $N = 182$	Digestive $N = 73$	Urinary $N = 107$	Cellulitis $N = 168$	Septicaemia $N = 34$
Age (years) $^{*R\,D\,C\,S}$	45.5 (18.4)	34.0 (13.0)	38.0 (17.4)	40.4 (15.5)	48.8 (15.9)
Male % $^{*D\,U}$	95 (52.2)	23 (31.5)	90 (84.1)	84 (50.0)	17 (50.0)
Aboriginal %	121 (66.5)	40 (54.8)	69 (64.5)	91 (54.2)	17 (50.0)
WC (cm) ^{*C}	95.3 (17.2)	96.1 (16.6)	95.8 (17.5)	100.0 (18.6)	106.8 (16.5)
BMI (kg/m^2) $^{*R\,C\,S}$	26.7 (7.1)	27.7 (7.0)	27.4 (7.4)	29.1 (8.0)	31.3 (8.2)
SBP (mmHg) $^{*R\,D\,C\,S}$	134.3 (24.4)	124.5 (19.8)	127.7 (20.1)	132.6 (21.0)	149.4 (24.1)
DBP (mmHg) $^{*R\,S}$	73.9 (14.9)	68.8 (12.9)	69.7 (12.2)	72.1 (13.4)	77.7 (14.5)
Cholesterol (mmol/L) ^{*U}	4.9 (1.1)	4.8 (1.0)	4.7 (1.1)	4.9 (1.1)	5.1 (1.1)
HDLC (mmol/L) $^{*D\,U}$	1.2 (0.4)	1.1 (0.2)	1.1 (0.3)	1.1 (0.3)	1.0 (0.3)
Median Triglycerides (mmol/L) ^{*D}	1.8 (1.8)	1.3 (1.5)	1.5 (1.2)	2.1 (1.9)	2.5 (1.8)
BMI ≥25%	103 (56.6)	45 (61.6)	60 (56.1)	102 (60.7)	26 (76.5)
Hypertension% $^{*R\,C}$	71 (39.0)	17 (23.3)	25 (23.4)	59 (35.1)	22 (64.7)
Smokers % $^{*D\,U\,S}$	119 (69.6)	56 (76.7)	71 (67.0)	86 (52.4)	12 (35.3)
Alcohol drinkers %	110 (62.9)	55 (76.4)	65 (61.9)	116 (69.9)	18 (56.3)
PA enough %	39 (21.4)	59 (80.8)	90 (84.1)	36 (21.4)	6 (17.7)

Number in the table showing mean (SD) or n (%);
$^{*}P < 0.05$ from t test or chi-square test or the corresponding non-parametric tests of Mann–Whitney test or Fisher's exact test; $^{R\,D\,C\,S}$ indicating significant difference by categories of "Respiratory/ENT" "Digestive" "Urinary" "Cellulitis" "Septicaemia"

Table 5
7-year follow up risk of hospitalized infections associated with diabetes/glucose (odds ratio and 95% CI).

	RR	Diabetes	Glucose 4.7–5.2	Glucose ≥5.3 mmol/L
Respiratory/ENT	Crude	1.5 (1.1–2.2)	0.9 (0.7–1.4)	1.3 (1.0–1.9)
	Adjusted	1.2 (0.8–1.7)	0.8 (0.6–1.2)	1.0 (0.7–1.5)
Digestive	Crude	1.0 (0.5–1.9)	0.7 (0.4–1.2)	0.6 (0.4–1.1)
	Adjusted	1.1 (0.5–2.2)	0.8 (0.4–1.4)	0.8 (0.4–1.4)
Urinary	Crude	2.7 (1.8–4.0)	1.1 (0.7–1.8)	1.6 (1.1–2.4)
	Adjusted	3.6 (2.2–5.7)	1.3 (0.8–2.1)	2.1 (1.3–3.5)
Cellulitis	Crude	3.1 (2.3–4.2)	0.7 (0.4–1.0)	1.7 (1.2–2.3)
	Adjusted	2.9 (2.0–4.1)	0.6 (0.4–1.0)	1.4 (1.0–2.1)
Septicaemia	Crude	6.0 (3.1–11.7)	1.0 (0.4–3.1)	3.3 (1.4–7.7)
	Adjusted	3.3 (1.6–6.8)	0.7 (0.2–2.1)	1.2 (0.5–3.1)
Overall	Crude	2.4 (1.8–3.0)	0.9 (0.7–1.1)	1.4 (1.1–1.8)
	Adjusted	2.1 (1.6–2.8)	0.8 (0.6–1.1)	1.2 (0.9–1.6)

Risk ratios from GLM with family as binomial and link as log;
The reference for the models by diabetes being "no" and by glucose being lst tertile of <4.7 mmol/L.
The adjusted RRs from models included age, gender, ethnicity, baseline BMI, hypertension, lipid, smoking and drinking

average that 16% of this Indigenous diabetic cohort from remote northern Australian communities were hospitalized each year for severe infection over a seven year period, and was approximately double that of the non-diabetic cohort. This rate is 10 times higher than an urban non-Indigenous Australian cohort (Hamilton et al., 2013) which found 20% of those with diabetes were hospitalized with infection over a 12 year period (1.67% per year on average). Further, we found that length of hospital stay was nearly double for patients with diabetes, suggesting more severe disease or reduced responsiveness to treatment or both. A large Canadian study in patients with unspecified diabetes compared to matched controls sourced from administrative data found a similar doubling of risk for infection-related hospitalization and deaths from infections (Shah & Hux, 2003).

We found the most frequently hospitalized infections were cellulitis followed by urinary, digestive infections mainly cholecystitis, and lastly septicaemia. Skin and soft tissue infection is highly prevalent among Australian Indigenous children especially in remote areas (Clucas et al., 2008). Socioeconomic status and poor housing contribute to the spread of these infections (Bailie et al., 2005). The most frequent pathogens causing skin infection in children were group A streptococcus and *Staphylococcus aureus* (Valery et al., 2008) so it is therefore not surprising that cellulitis was common in adults.

Severe urinary tract infection was also highly prevalent in this cohort and having diabetes amplified this risk 3-fold. This is a similar pattern to that from studies in US (Fu et al., 2014) and UK (Hirji, Guo, Andersson, Hammar, & Gomez-Caminero, 2012) reporting a relative risk of two among adults with diabetes for UTI compared to matched controls. Direct comparisons with our cohort are not possible as the Canadian and UK studies used population-based registration data.

Strengths of this study include a broadly representative community-based sample of both Aboriginal and Torres Strait Islander adults from remote sites, objective baseline clinical measurements and a cohort design. Limitations include a relatively short follow up period, lack of detailed medical and family history and potential unmeasured confounding factors. Hospitalization data for people moving away from the study area were not always accessible and the hospital admission data were potentially prone to coding errors.

In summary, we found an extremely high absolute risk for serious community-acquired infection in this Indigenous cohort from north Queensland remote communities, and that having diabetes doubled this risk and resulted in more severe illness and longer hospital stays. Improving community housing conditions and opportunities to control spread of infection more generally would reduce the high background rates of severe infection. The high prevalence of diabetes in these communities, where up to half of all adults are affected, means that there will also be high absolute numbers of infections with increased severity. Pro-active and aggressive management of early infection, especially cellulitis, in people with diabetes through the primary care service can reduce complications, including hospitalization for infections (McDermott & Segal, 2006).

Table 6
Total LOS (days) of hospitalization of infections by diabetes status.

	No diabetes $n = 2391$		Diabetes Yes $n = 396$		p
	No.	Median (IQR)	No	Median (IQR)	
Respiratory/ENT	145	3 (2–6)	37	4 (3–7)	0.02
Digestive	63	3 (1–4)	10	5 (3–14)	0.04
Urinary	74	2.5 (2–4)	33	4 (2–6)	0.04
Cellulitis	111	3.5 (2–6)	57	5 (3–11)	0.001
Septicaemia	17	7 (5.5–18)	17	8 (6–12.5)	0.836
Overall	348	3.4 (2–6.4)	113	6 (4–13)	<0.001

P from Mann–Whitney U test

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Appendix A

Table A1
Characteristics of Indigenous participants in North Queensland during 1998–2007.

	Not hospitalized $N = 1034$	Hospitalized $N = 1753$	Total $N = 2787$
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)
Age (years)	36.0 (14.2)	37.7 (15.9)	37.1 (15.3)
Male %	460 (44.5)	988 (56.4)	1448 (52.0)
Aboriginal %	604 (58.4)	1037 (59.2)	1641 (58.9)
WC (cm)	95.0 (16.6)	95.6 (16.9)	95.4 (16.8)
BMI (kg/m^2)	27.8 (7.0)	27.6 (7.2)	27.7 (7.1)
SBP (mmHg)	129.4 (17.0)	129.9 (20.6)	129.7 (19.3)
DBP (mmHg)	71.3 (12.8)	71.1 (13.9)	71.2 (13.5)
Fasting glucose (mmol/L)	5.5 (2.2)	5.8 (2.8)	5.7 (2.6)
Cholesterol (mmol/L)	5.0 (1.0)	4.9 (1.1)	4.9 (1.1)
HDLC (mmol/L)	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)
Median triglycerides (mmol/L)	1.3 (0.9–2.0)	1.4 (0.9–2.1)	1.4 (0.9–2.1)
BMI ≥25%	641 (62.0)	1061 (60.5)	1702 (61.1)
Hypertension %	282 (27.3)	508 (29.0)	790 (28.4)
Diabetes %	119 (11.5)	277 (15.8)	396 (14.2)
Smokers %	569 (55.4)	1027 (59.0)	1596 (57.7)
Alcohol drinkers %	702 (70.8)	1167 (68.5)	1869 (69.3)
PA enough %	269 (26.0)	386 (22.0)	655 (23.5)

Hypertension was ascertained either by detection of high BP at examination (measured BP >140/90 mmHg) or previous confirmed diagnosis or currently prescribed antihypertensive medication;
Diabetes was defined as either clinical diagnosis verified by the participants' medical records or a 2 hour glucose tolerance test or fasting blood glucose level >7.0 mmol/L.
Physical activity was defined using the WHO criteria in which 'enough' means doing moderate to vigorous physical activity for more than 30 min/d for 5 days.

Table A2
Number (%) of people hospitalized with selected infections by glucose tertiles.

	1st tertile (<4.7) $n = 990$	2nd tertile $n = 814$	3rd tertile (≥5.3) $n = 898$	p
Respiratory/ENT	59 (6.0)	46 (5.6)	72 (8.0)	0.091
Digestive	33 (3.3)	19 (2.3)	19 (2.1)	0.210
Urinary	31 (3.1)	28 (3.4)	44 (4.9)	0.108
Cellulitis	53 (5.3)	29 (3.6)	82 (9.1)	<0.001
Septicaemia	7 (0.7)	6 (0.7)	21 (2.3)	0.002
Overall	152 (15.4)	109 (13.4)	186 (20.7)	<0.001

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