The interaction between pre-operative anaemia and peri-operative blood transfusion on patient outcomes following general surgical procedure: a retrospective review

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ABSTRACT

AIM: To assess the incidence of pre-operative anaemia in patients presenting for general surgery and determine the relationship between pre-operative anaemia, transfusion and post-operative metrics including length of stay (LOS) and infectious complications.

METHOD: A retrospective cohort of 1,186 patients. Stratification into two groups with and without pre-operative anaemia through propensity score matching. Logistic regression was used to determine the relationship between pre-operative anaemia, blood transfusion and infectious complications.

RESULTS: The incidence of pre-operative anaemia was 17.4%. Red blood cell (RBC) transfusion was greater in those with PA than those without, 13.1% versus 0.7% (OR 21.7 (2.9–166.7, p<0.001)). In the propensity matched cohort, pre-operative anaemia was associated with an increase in LOS from 2.1 to 3.0 days (p=0.006) and increased infectious complications from 6.4% to 18.4%, (OR 3.3 (1.4–7.7), p=0.004). The risk of infectious complications was amplified in the patients receiving RBC transfusion. After adjustment for transfusion, in patients with pre-operative anaemia the OR for infectious complications became 2.3 (0.95–5.7, p=0.06) for those not transfused and 5.5 (2.0–15.3, p=0.001) for those transfused.

CONCLUSION: Pre-operative anaemia is associated with an increase in hospital LOS and infectious complications. When adjusted for transfusion the effect of pre-operative anaemia alone on hospital LOS and infectious complications is not statistically significant. Expeditious investigation and treatment of PA could reduce complications and save resources.

Pre-operative anaemia is common before major surgery. Anaemia is often multifactorial, particularly in those with cancer, in elderly or malnourished patients and in those with auto-immune and pro-inflammatory conditions.[1] The World Health Organization (WHO) defines anaemia as insufficient red cell mass to meet the body's physiological needs, with a haemoglobin (Hb) threshold of <130g/L in men and <120g/L in non-pregnant women.[2]

Anaemia in patients undergoing major surgery has been recognised as a problem which needs to be addressed. The 30-day morbidity and mortality in anaemic patients is greater than in those with normal haemoglobin levels pre-operatively.[3] The presence of pre-operative anaemia independently predicts the need for blood transfusion and increases the risk of post-operative infectious complications. Anaemia may also increase the costs associated with

healthcare through prolongation of length of stay, and the expenses associated with increased need for blood transfusion or blood procurement.[3] Furthermore, blood transfusion itself also increases post-operative mortality and morbidity including wound infection, pneumonia and sepsis through modulation of the immune system or inducing a procoagulant state.[1]

Pre-operative anaemia is an important modifiable risk factor. The Australian National Blood Authority recommends that healthcare providers establish programmes to optimise pre-operative haemoglobin, coagulation status and minimise blood loss.[1] These evidence-based initiatives aim to avoid exposing patients to potential harm from both anaemia and exposure to blood transfusion. Patients at increased risk of anaemia should have pre-operative haemoglobin and iron studies performed and receive timely treatment with iron or erythropoietin, if appropriate.[1,4] In patients with pre-operative anaemia undergoing colorectal surgery, pre-operative treatment with iron increases haemoglobin level and is associated with reduced need for blood transfusion.[5,6]

The purpose of this study is to delineate the prevalence of anaemia in a patient population presenting for general surgical procedures at Counties Manukau Health (CMH) and to determine the interaction between pre-operative anaemia, blood transfusion and post-operative metrics including length of stay (LOS) and infectious complications. This information will help to plan future initiatives to reduce the burden of pre-operative anaemia and rationalise blood produce use in the peri-operative period.

Method

Ethics

An exemption from formal Health and Disability Ethics Committee (HDEC) review was obtained as the project was out of scope. Institutional approval from the CMH Research Review Committee (number 164) was granted prospectively.

Aims

The aims were to determine the relationship between pre-operative anaemia and blood transfusion in patients undergoing either elective or emergency general surgical procedures at CMH. Specific outcomes include hospital LOS and peri-operative infectious complications defined through ICD-10 discharge coding (see Appendix 1).

Study design and population

This is a retrospective cohort study of both elective and emergency patients presenting for general surgical procedures at CMH between 1 January and 31 December 2015. A one-year period was chosen for convenience. We considered our sample to be large enough to include a representative spectrum of our population and practice. Patients over the age of 16 years presenting for either elective or emergency general surgical procedures during the study period were eligible for inclusion. Patients were excluded if they were having surgery under local anaesthesia (LA) alone, or if pre-operative haemoglobin was not measured within the 30 days before surgery. Patients meeting the above criteria were identified using their National Health Index (NHI) number through the Patient Information Management System (PiMS).

Data collection

Demographic data was collected from the hospital electronic data warehouse managed by the HealthAlliance including age, sex, American Association of Anesthesiology (ASA) score, ethnicity, ICD-10 comorbidity and ICD-10 complication codes, surgical venue, procedure name and duration, hospital length of stay, readmission to hospital at 30- and 90-days post-discharge and mortality.

Blood test results including Hb and creatinine were electronically extracted from the hospital DELPHIC and ÉCLAIR systems. We identified pre-operative haemoglobin and creatinine recordings within 30 days prior to surgery. The value closest to the date and time of surgery served as the surrogate for the pre-operative value for the purpose of statistical analyses as outlined below. Pre-operative measurement of haemoglobin is guided by local guidelines, with oversight from the Choosing Wisely campaign, which aim to rationalise blood testing. The administration of blood products was determined from the DELPHIC system. Blood products were defined as packed red blood cells (RBC), fresh frozen plasma (FFP), platelets, cryoprecipitate and human albumin.

Analysis and statistics

Data was stored in a Microsoft Excel spreadsheet. All statistical analyses were performed using SPSS statistics software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Results are presented as number (percent), median (interquartile range) and odds ratios (OR) (95th percent confidence interval) as appropriate. Propensity score matching by age, sex, ethnicity, ASA score, surgical duration and pre-operative creatinine was performed to obtain two balanced cohorts with and without pre-operative anaemia. These factors were chosen as potential confounders of risk factors for anaemia and threshold for transfusion. Pre-operative anaemia was defined as Hb <120g/L in females and <130g/L in males as per the most recent WHO criteria.[2] Haemoglobin levels of 110–119, 80–109 or <80g/L are used to categorise severity of anaemia in non-pregnant women as mild, moderate or severe respectively. In men, haemoglobin levels of 110–129, 80–109 or <80 g/L are used. Logistic regression was used to determine the relationship between pre-operative anaemia, blood transfusion and infectious complications. Comparisons were made with the Fisher Exact test and the Mann-Whitney U-test for categorical and continuous variables respectively. A two-tailed p-value of $p<0.05$ defined statistical significance.

Results

During the study period, 2,537 patients underwent general surgical procedures. Of these, 1,186 were excluded leaving 1,351 patients. Reasons for exclusion were; 164 patients having surgery under LA alone and 1,022 patients without a pre-operative Hb recording. In those where a pre-operative haemoglobin measurement available, 236/1,351 (17.5%) were anaemic by the standard WHO definition (see Figure 1). The overall mortality rate at 30 days was 0.12% (3/2,537) and 1.58% (40/2,537) at one year.

Propensity score matching to account for age, sex, ethnicity, ASA score, surgical duration and pre-operative creatinine was possible for 61.4% of patients using a match tolerance of 0.001. This produced two balanced cohorts with and without pre-operative anaemia, each with 145 patients (see Table 1).

Incidence and severity of pre-operative anaemia

The distribution of severity of anaemia is seen in Table 2. Severity of anaemia was classified as per the most recent WHO definitions appropriate to patient sex.[7]

Pre-operative anaemia and length of stay

In the propensity matched patients, pre-operative anaemia was associated with increase in median hospital LOS from 2.1 days (IQR 1.2–3.2) to 3.0 days (1.2–6.3)

Figure 1: Patient flow.

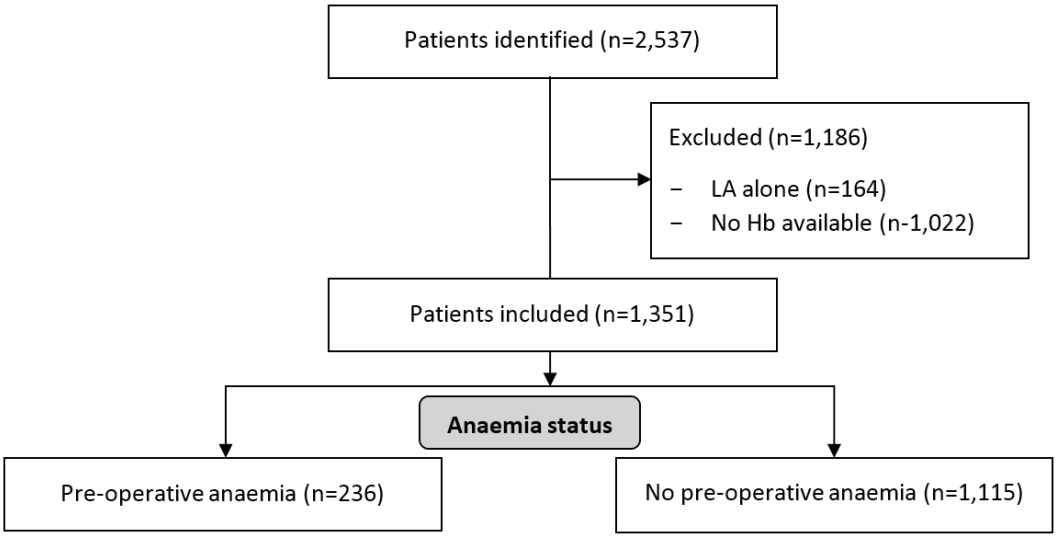

Table 1: Results of propensity score matching.

		Anaemia (n=145)	**No anaemia** (n=145)	**p-value**
Sex N (%)	Female	78 (53.8)	91 (62.8)	0.12
	Male	67 (46.2)	54 (37.2)	
Ethnicity N (%)	Asian	15 (10.3)	8 (5.5)	0.41
	European	65 (44.8)	79 (54.5)	
	Indian	6 (4.1)	7 (4.8)	
	Māori	17 (11.7)	19 (13.1)	
	Pacific Island	33 (22.8)	25 (17.2)	
	Other	9 (6.2)	7 (4.8)	
ASA Score N (%)	1	16 (11.0)	28 (19.3)	0.29
	2	71 (49.0)	71 (49.0)	
	3	53 (36.6)	43 (29.7)	
	4	4 (2.8)	2 (1.4)	
	Not recorded	1 (0.7)	1 (0.7)	
Surgical time Minutes	Median	114	119	0.63
	IQR	79–179	82–265	
Closest creatinine Mmol/L	Median	74	72	0.79
	IQR	65–91	65–86	
Age Years	Median	60	57	0.31
	IQR	47–71	42–67	

(p=0.006). The LOS in patients with mild pre-operative anaemia was similar to those with no evidence of pre-operative anaemia (p=1.00), whereas in those with moderate (p<0.001) and severe pre-operative anaemia (p=0.04) the LOS was significantly prolonged compared with those without pre-operative anaemia.

Pre-operative anaemia and infectious complications

Information on infectious complications was available for 125 patients from each of the propensity matched groups. Pre-operative anaemia was associated with an increase in overall infectious complications from 6.4% to 18.4% (OR 3.3 (1.4–7.7)

Table 2: Severity of anaemia in the propensity matched patients.

Mild		**Moderate**		**Severe**	
N =	%	N =	%	N =	%
87	60.0%	55	37.9%	3	2.1%

Table 3: Infectious complications by anaemia status in the propensity matched groups.

	Anaemia (n=125)		**No anaemia** (n=125)		
	N=	%	N=	%	p-value
Infectious complications	23	18.4	8	6.4	0.004
Wound infections	6	4.8	0	0.0	0.013
Sepsis	10	8.0	2	1.6	0.018

p=0.004). There was an increase in sepsis in the group with pre-operative anaemia from 1.6% to 8.0% (OR 5.4 (1.2–25.0) p=0.018). There was also an increase in wound infections in those with pre-operative anaemia compared to those without, 4.8% versus 0% (p=0.013). See Table 3.

Rate of transfusion

In the overall cohort the rate of RBC transfusion was 19.1% (45/236) in those with pre-operative anaemia, and 0.6% (7/1,115) in those without (p<0.001). The OR for RBC transfusion in the presence of pre-operative anaemia was 37.0 (16.7–83.3, p<0.001). The use of individual blood products (namely FFP and cryoprecipitate) was significantly increased in those with pre-operative anaemia. Likewise, for a composite measure encompassing the use all blood products, the rate of transfusion was again increased in those with pre-operative anaemia 22.5% (53/236) compared to those without 1.3% (14/1,115) (p<0.001).

RBC transfusion in the propensity matched cohort was greater in the group with pre-operative anaemia 13.1% versus 0.7%, OR 21.7 (2.9–166.7, p<0.001) (see Table 4). Exposure to all blood products was greater in the group with pre-operative anaemia. When blood product use was analysed separately, this difference was driven by RBC use between the groups.

RBC transfusion and infectious complications

Using logistic regression, the effect of RBC use on infectious complications was examined. After adjustment for both RBC transfusion and pre-operative anaemia the OR for overall infectious complications in those with pre-operative anaemia became 2.3 (0.95–5.7, p=0.06), while OR for infectious complications in those transfused RBC was 5.5 (2.0–15.3, p=0.001).

Discussion

We have shown that pre-operative anaemia is common and leads to an increased hospital length of stay of approximately 20 hours in a population of patients undergoing elective and emergency general surgical procedures at a tertiary New Zealand Hospital. Patients with pre-operative anaemia had an increased risk of infectious complications with a concurrent increased exposure to red blood cell transfusion. However, when these results were adjusted for the effect of red blood cell transfusion, this factor had greater significance than anaemia alone. These results have obvious implications for the provision of peri-operative care, especially in those undergoing procedures associated with significant blood loss and transfusion exposure.

Table 4: Transfusion in the propensity matched groups.

	Anaemia		**No anaemia**		
	N=	%	N=	%	p-value
Any blood product transfused	22	15.2	4	2.8	<0.001
RBC transfusion	19	13.1	1	0.7	<0.001

Table 5: Infectious complications by transfusion in the propensity matched groups.

	No RBC transfusion		RBC transfusion		
	N=	%	N=	%	p-value
Infectious complications	22	9.6	9	45.0	<0.001
Wound infections	4	1.7	2	10.0	0.075
Sepsis	7	3.0	5	25.0	0.001

Pre-operative anaemia is a highly prevalent condition with the rate varying by age, ethnicity, the type of surgery, whether surgery is elective or emergent and by patient comorbidities. A 2011 analysis of the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) database reported that pre-operative anaemia was seen in 28.9% of general surgical patients.[3] Larger cohorts looking at patients undergoing all forms of non-cardiac surgery have found the prevalence of anaemia to be approximately 30%.[8,9] These studies have also demonstrated a relationship between pre-operative anaemia and adverse perioperative outcomes, particularly infectious complications, which was echoed in this study. The slightly lower incidence of pre-operative anaemia of 17.5% identified in our study is possibly attributable to differences in the patients included. Our cohort was younger and included a higher proportion of patients with lower ASA scores than the aforementioned studies. However, our figure is in line with the prevalence of pre-operative anaemia across all surgical specialties of 14–20% quoted in Western Australia.[10]

The fact that blood transfusion is associated with increased morbidity and mortality is now well recognised and widely reported.[11] Furthermore, the increase in adverse outcomes with blood transfusion is dose dependent, the exact mechanism for these findings has not been fully elucidated.[12] This may be related to modulation of the immune system or the activation of an inflammatory response which presents a paradox given desired effect of RBC transfusion is to increase the blood haemoglobin level to reverse the anaemia and to increase arterial blood oxygen. There is evidence from randomised controlled trials linking blood transfusion and infectious complications.[11] Given the strong link between pre-operative anaemia, RBC transfusion and the similar complication profiles induced by both conditions, further investigation is required to determine the risks attributable to each and potential strategies to alleviate these risks. Others have shown that anaemia alone is associated with increases in infectious complications, whereas in the current study it appears that transfusion rather than anaemia is a greater driver.[3,8]

Pre-operative anaemia is a strong predictor of the need for blood transfusion. We found that in patients presenting for general surgery, after adjusting for potential confounders, that RBC transfusion was more frequent in those with pre-operative anaemia. Both pre-operative anaemia and transfusion can contribute to poor outcomes due to the links between these parameters. Given this information the financial implications of both anaemia and transfusion should be investigated further.

The WHO defines anaemia as a haemoglobin below 130g/L in males and 120g/L in females. These definitions were first disseminated in 1968 and have since been refined to include specific thresholds for neonates, children of different ages and for the parturient. This definition now also includes mild, moderate and severe sub-classifications. The key effect of anaemia on human physiology is the reduction in oxygen transport and delivery to the tissues, which can lead to anaerobic metabolism in circulations with fragile or impaired blood supplies. This can lead to impaired wound healing and wound infections. The objective of an allogeneic blood transfusion is to increase the circulating red cell mass with a concurrent increase in the haemoglobin level to improve cellular oxygen delivery.

There is now evidence to suggest that the transfusion of allogeneic blood does not achieve these goals in the short-term. This may be related to decreased red cell deformability in capillary beds and to the changes in the oxygen-haemoglobin dissociation curve induced by the storage of blood. Lysis of transfused red cells and the resultant release of free haemoglobin may also serve as a trigger for the induction of inflammatory responses, which may contribute to the observed morbidity and mortality seen following red blood cell transfusion.[13]

Following propensity score matching we found an increase in hospital length of stay of approximately 20 hours in patients with pre-operative anaemia. Although this figure by itself is not especially impressive, when combined with the cost associated with red blood cell transfusion and the increase in infectious complications seen with both anaemia and blood transfusion scaled to the total number of discharges each year following general surgical procedures across all public hospitals in New Zealand (of which there were 44,502 in 2018),[14] the costs associated with anaemia could become considerable. A secondary analysis of the European Surgical Outcomes Study (EuSOS) found a similar increase in length of hospitalisation and number of intensive care unit (ICU) admissions in patients with pre-operative anaemia undergoing non-cardiac surgery.[8] Furthermore, hospital length of stay and ICU admission rates increased with increasing severity of pre-operative anaemia.[8] The increased hospital expenditure generated by these additional bed days and higher level of care may provide financial incentives to introduce robust pre-operative anaemia screening and management clinics.[9,15]

At the core of a patient blood management (PBM) programme is the prevention of allogeneic blood transfusion. PBM programmes adopt an evidence-based approach to the expeditious investigation and treatment of pre-operative anaemia prior to planned surgical procedures as a multidisciplinary effort.[9] The National Blood Authority guidelines recommended healthcare services implement multidisciplinary, multimodal peri-operative patient blood management programmes.[1] These are the most commonly referred to guidelines in Australasia and are in line with other international recommendations.[16] They emphasise the need to improve pre-operative management of anaemic patients—in an ideal setting this assessment would take place more than two weeks before surgery to allow for any latency of treatment with agents such as iron or erythropoietin.[9,17] There is evidence to suggest that early intervention against anaemia is more cost-effective than treating the condition at the time of surgery with a red blood cell transfusion.[18,19] A recent study provided data on the implementation of PBM programmes in four Australian tertiary hospitals. They found that five years after the implementation of PBM programmes, the prevalence of pre-operative anaemia decreased from 20.8% to 14.4%, RBC transfusions decreased by 41% and there were savings of approximately one million dollars over the course of the programme.[10] Despite strong evidence, these initiatives remain uncommon in New Zealand, likely due to resource constraints.

Despite the obvious links between pre-operative iron deficiency anaemia and increased rates of perioperative red blood cell transfusion and impaired perioperative outcomes, there is minimal evidence to suggest that the treatment of iron deficiency anaemia with oral or intravenous iron can lead to improved post-operative outcomes.[17] This may relate to an insufficient treatment window before surgery or the provision of iron in oral form, which is poorly tolerated and not readily absorbed.[17] The lack of outcome data, combined with both the financial and time investment required to establish a robust, multidisciplinary patient blood management programme has meant that uptake has been slow.[9] In 2019 several large prospective studies are scheduled to report their results, which may provide some direction as to whether the identification and treatment of iron deficiency anaemia is a sound use of resources in an era of fiscal constraint.

Our study has several limitations. The retrospective nature reduced the ability to collect some forms of data, meaning that our ability to control for all potential confounding factors was reduced. We were reliant on the accuracy of the routinely collected data from PiMS, laboratory testing and blood transfusion databases. The

data authenticity was reviewed to remove truly spurious values (eg, incorrect year of surgery) however on an individual patient level there was minimal capacity to review paper records to ensure that ICU admissions or additional complications were not missed. This is a single-centre study conducted over a period of 12 months which provides a snapshot of our service provision and patient outcomes, which may not be applicable to other centres due to differences in patient demographics such as ethnicity or patient age.

Patients were only included where a pre-operative haemoglobin recording was available within 30 days before surgery. This may have led to the exclusion of younger and more healthy patients who did not meet criteria for preoperative laboratory testing, meaning our results are skewed towards an older and more comorbid cohort. A report from the ACS-NSQIP database found a haemoglobin recording in more than 90% of patients four weeks before surgery, whereas in the current series only 60% of patients possessed a haemoglobin value in the same time window. This may reflect differing thresholds for investigation prior to surgery between countries. Our data does not differentiate between the numerous causes of anaemia. There are numerous acute and chronic disease processes where iron use may be contraindicated. The WHO definitions of anaemia used in this study have been subject to recent debate around the validity of the chosen thresholds and whether sex-specific differences should continue to exist.[9,20] We chose to use the existing WHO definitions of anaemia to be consistent with other literature in this area.

The use of propensity score matching has given us additional control over potential confounders. We chose to match patient pairs by age, sex, ethnicity, renal function, surgical duration and ASA score to produce two matched cohorts which were stratified by the presence or absence of anaemia. We chose to use surgical duration as a surrogate for operative severity due to frequent errors in coding. Other studies have identified surgical duration as a predictor of infectious complications and increased hospital LOS.[21,22] This was included in the propensity match to reduce confounding. Each of these factors are important predictors of surgical outcomes and in some cases may be linked to the rate of anaemia (eg, those with severe renal dysfunction). By balancing these factors our ability to detect differences in outcomes in relation to the presence or absence of anaemia is enhanced. The use of a precise match tolerance limited the size of the propensity score matched groups. This reduces the power of the analysis. By only selecting one surgical speciality we were able to somewhat reduce the number of potential procedures which were included, making our results more applicable to this patient group.

Conclusion

We have identified a significant burden of anaemia in a patient population undergoing general surgical procedures at a tertiary New Zealand hospital. Anaemia is strongly associated with red blood cell use, which in turn is a significant predictor of adverse post-operative outcomes. Importantly, we found that the effect of blood transfusion was of greater significance to infectious complications than anaemia itself.

This study adds to the body of literature supporting the establishment of pre-operative programmes designed to diagnose, investigate and optimise anaemia prior to surgery. The expeditious management of anaemia without resorting to blood transfusion could prevent complications and save resources. We plan to investigate these findings across other surgical specialities to further refine the risks associated with pre-operative anaemia.

Appendix 1: ICD-10 Infectious Complication Codes

A047	Enterocolitis due to Clostridium difficile
A099	Gastroenteritis and colitis of unspecified origin
A402	Sepsis due to streptococcus, group D
A408	Other streptococcal sepsis
A410	Sepsis due to Staphylococcus aureus
A411	Sepsis due to other specified staphylococcus
A414	Sepsis due to anaerobes
A4151	Sepsis due to Escherichia coli [E. Coli]
A4152	Sepsis due to Pseudomonas
A4158	Sepsis due to other Gram-negative organisms
A418	Other specified sepsis
A419	Sepsis, unspecified
A428	Other forms of actinomycosis
A4901	Staphylococcus aureus infection, unspecified site
A491	Streptococcal infection, unspecified site
A498	Other bacterial infections of unspecified site
B948	Sequelae of other specified infectious and parasitic diseases
B950	Streptococcus, group A, as the cause of diseases classified to other chapters
B951	Streptococcus, group B, as the cause of diseases classified to other chapters
B952	Streptococcus, group D, as the cause of diseases classified to other chapters
B9541	Streptococcus, group C, as the cause of diseases classified to other chapters
B9548	Streptococcus, other specified group, as the cause of diseases classified to other chap-ters
B956	Staphylococcus aureus as the cause of diseases classified to other chapters
B957	Other staphylococcus as the cause of diseases classified to other chapters
B961	Klebsiella pneumoniae [K. pneumoniae] as the cause of diseases classified to other chapters
B962	Escherichia coli [E. coli] as the cause of diseases classified to other chapters
B9639	Haemophilus influenzae [H. influenzae] type not specified, as the cause of diseases classified to other chapters
B964	Proteus (mirabilis)(morganii) as the cause of diseases classified to other chapters
B965	Pseudomonas (aeruginosa) as the cause of diseases classified to other chapters
B966	Bacillus fragilis [B. fragilis] as the cause of diseases classified to other chapters
B9688	Other and unspecified bacterial agents as the cause of diseases classified to other chap-ters
B977	Papillomavirus as the cause of diseases classified to other chapters
B978	Other viral agents as the cause of diseases classified to other chapters

B99	Other and unspecified infectious diseases
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J150	Pneumonia due to Klebsiella pneumoniae
J151	Pneumonia due to Pseudomonas
J155	Pneumonia due to Escherichia coli
J156	Pneumonia due to other (aerobic) Gram-negative bacteria
J180	Bronchopneumonia, unspecified
J181	Lobar pneumonia, unspecified
J189	Pneumonia, unspecified
J22	Unspecified acute lower respiratory infection
L0302	Cellulitis of toe
L0310	Cellulitis of upper limb
L0311	Cellulitis of lower limb
L032	Cellulitis of face
L033	Cellulitis of trunk
L038	Cellulitis of other sites
L020	Cutaneous abscess, furuncle and carbuncle of face
L022	Cutaneous abscess, furuncle and carbuncle of trunk
L023	Cutaneous abscess, furuncle and carbuncle of buttock
L024	Cutaneous abscess, furuncle and carbuncle of limb
L028	Cutaneous abscess, furuncle and carbuncle of other sites
L088	Other specified local infections of skin and subcutaneous tissue
L089	Local infection of skin and subcutaneous tissue, unspecified
M8696	Unspecified osteomyelitis, lower leg
M8697	Unspecified osteomyelitis, ankle and foot
N300	Acute cystitis
N308	Other cystitis
N309	Cystitis, unspecified
R650	Systemic inflammatory response syndrome [SIRS] of infectious origin without acute organ failure
R651	Systemic inflammatory response syndrome [SIRS] of infectious origin with acute organ failure
R652	Systemic inflammatory response syndrome [SIRS] of noninfectious origin without acute organ failure
R653	Systemic inflammatory response syndrome [SIRS] of noninfectious origin with acute organ failure
T845	Infection and inflammatory reaction due to internal joint prosthesis

T846	Infection and inflammatory reaction due to internal fixation device [any site]
T847	Infection and inflammatory reaction due to other internal orthopaedic prosthetic devices, implants and grafts
T8578	Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts
T8141	Wound infection following a procedure
T8142	Sepsis following a procedure
T835	Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system
T836	Infection and inflammatory reaction due to prosthetic device, implant and graft in genital tract

Competing interests:
Dr Lightfoot reports personal fees from Merck Sharp and Dohme outside the submitted work.

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