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PHARMACOEPIDEMIOLOGY OF QT-INTERVAL PROLONGING DRUG ADMINISTRATION IN CRITICALLY ILL PATIENTS

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Abstract

Purpose—Commonly prescribed medications produce QT-prolongation and are associated with *torsades de pointes* in non-acutely ill patients. We examined patterns of QT-prolonging drug use in critically ill individuals.

Methods—An administrative critical care database was utilized to identify patients receiving drugs associated with QT-interval prolongation or *torsades de pointes* for ≥24 hours.

Results—Data from 212,016 individuals collected over a 63-month period was examined to identify 6,125 patients (2.9%) receiving QT-interval prolonging drugs. These individuals had a mean (±SE) age of 63.0 (±0.2) years, were predominately male (55.4%) and Caucasian (84.4%), and were exposed to QT-interval prolonging agents for a mean (±SE) 53.1 (±0.4) % of their ICU length of stay. Respiratory and cardiovascular illnesses were the most common reasons for ICU admission (17.2%, 12.0%, respectively). The most frequently administered agents were Amiodarone (23.5%), Haloperidol (19.8%), and Levofloxacin (19.7%); no other single agent accounted for more than 10% of QT-interval prolonging drugs prescribed. Coadministration of QT-prolonging drugs occurred in 1,139 patients (18.6%). These patients had higher ICU mortality rate and longer ICU lengths of stay, compared to patients not receiving coadministered drugs ($p<0.001$ for both). For patients receiving coadministered drugs, overlap occurred for 71.4 (±0.8) % of the time that the drugs were given. Amiodarone coadministration with antibiotics, Haloperidol coadministration with antibiotics, and Haloperidol coadministration with Amiodarone, comprised 15.2%, 13.7%, and 9.4%, of all coadministered agents, respectively.

Conclusions—QT-prolonging drugs were used in a minority of critically ill patients. Prospective evaluation in the ICU environment is necessary to determine whether administration of these agents is associated with adverse cardiac events comparable to those reported in ambulatory patients.

MeSH terms

arrhythmia; drug toxicity; database; critical care; intensive care; pharmacoepidemiology

Introduction

Many commonly prescribed medications produce QT-interval prolongation and are associated with increased risk of ventricular tachyarrhythmia, specifically *torsades de*

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pointes (1–4). Such toxicity is one of the most common causes of pharmaceutical restriction or withdrawal following regulatory approval(1;5;6). Pro-arrhythmic potential appears most pronounced when agents are prescribed in the setting of factors predisposing to arrhythmia (e.g., coronary ischemia or electrolyte abnormality), when used in conjunction with drugs impairing metabolism, or when coadministered with pharmaceuticals possessing similar QT-interval prolonging properties(1;3;5;7).

While studies examining patterns and effects of QT-interval prolonging drug use have focused on non-acutely ill patients, this phenomenon is relevant to intensivists. Many agents implicated, such as antibiotics, antiarrhythmics, and antipsychotics, are frequently prescribed in the intensive care setting(2;4;8–14). Further, polypharmacy is common practice in this environment, increasing the likelihood of untoward drug interaction(15). Finally, factors commonly encountered in the critically ill patient - pre-existing cardiac disease, shock, use of vasoconstrictive agents, organ failure, metabolic derangement, and fasting - may predispose to drug-induced arrhythmia(7). Untoward cardiac effects of QT-interval prolonging drugs might be quite pronounced in the setting of acute illness.

The purpose of this study was to profile QT-interval prolonging drug use in a large population of critically ill patients. We intend for this information to serve as a foundation for better understanding the factors that may predispose to drug induced arrhythmia in the ICU environment.

Materials and Methods

Description of *Project Impact* administrative database

Project Impact (Cerner Corporation, Kansas City, MO), an administrative critical care database, was the source of patient data for this study(16). This resource has been used in a number of investigations exploring many facets of ICU care(16–20). *Project Impact* contains descriptive information with respect to participating institutions including number of licensed hospital beds, hospital location, and whether the hospital is academically affiliated, for profit, or not for profit. Descriptive ICU information is also captured including type (medical, surgical, subspecialty), number of licensed beds, and staffing model (e.g., availability of intensivists and whether management by intensivists is mandatory). *Project Impact* contains anonymized clinical data including age, gender, ethnicity, payer status, and descriptions of chronic health conditions identical to that used in APACHE II scoring(21). Criteria for these conditions are as follows.

Gastrointestinal: biopsy proven cirrhosis and documented portal hypertension; episodes of prior gastrointestinal hemorrhage attributable to portal hypertension, prior episodes of hepatic failure, encephalopathy, or coma. *Respiratory*: Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction; documented chronic hypoxia, hypercapnia, secondary polycythemia or severe pulmonary HTN (>40mmHg); respirator dependency related to active respiratory disease such as sarcoidosis, interstitial fibrosis, TB, COPD. *Cardiovascular*: NY Heart Association Class IV, severe coronary artery disease, severe valvular heart disease, severe cardiomyopathy. *Renal*: receiving chronic renal replacement therapy; previously documented chronic renal insufficiency with the most recent serum creatinine >2.0 mg/dL. *Project Impact* categorizes patients as to 41 ICU admitting diagnostic categories (presented in Appendix 3). These categories are unique; a patient is assigned only one.

Identification and categorization of QT-interval prolonging medications

For the period of study, all patient records contained in our analysis file were queried to identify individuals receiving drugs associated with QT-interval prolongation and/or

torsades de pointes as reported by the Center for Education and Research on Therapeutics (CERT), a publically accessible, frequently updated web-based resource(4). (Table 1) Drugs in *Project Impact* are assigned a unique numeric code. CERT reports a nomenclature that stratifies drugs based on risk of drug-induced arrhythmia such that a designation of '*1*' denotes drugs that are generally accepted to have a risk of causing *torsades de pointes* while '*2*' denotes drugs that have reported association with *torsades de pointes* but for which substantial evidence is lacking(4). We utilized this nomenclature for our study. We limited our analysis to patients receiving these agents (enterally or parenterally) for at least 24 hours because we felt that this exposure represented the minimal clinical risk that we felt was sufficiently important to detect. For each drug, frequency of coadministration with other QT-interval prolonging agents was determined, analogous to prior reports(2). For the purposes of this study, we defined coadministration as simultaneous administration with an overlap of at least 24 hours duration. Analysis was limited to agents comprising ≥1% of all QT-interval prolonging drugs administered.

Statistical analysis

Continuous data were compared using either a two sample t-test or Wilcoxon two sample test as appropriate. Categorical data were compared using either Chi Square or Fisher's Exact Test as appropriate. Standard software was used for all computations (SYSTAT 11, Systat Software, Inc., Richmond, VA).

Human subjects protection

This study was approved by the Human Studies Committee of Washington University School of Medicine.

Results

Characteristics of hospitals and ICUs contained in dataset

We analyzed data collected from 61 hospitals over a 63-month period (January 2000 through March 2005). These hospitals had a median number of licensed beds of 489 (inter-quartile range (IQR): 342.25–636) and represented all American Hospital Association (AHA) regions with a predominance from the East North Central (24.6 %), South Atlantic (18.0 %), West North Central (13.1%), and New England (11.5%) districts. Most of these institutions were urban (54.1%) and non-academically affiliated. Only 14 university-based hospitals were represented (22.9%). (Additional detail regarding hospital characteristics is presented in Appendix 1).

The majority of the 76 ICUs sampled were mixed medical/surgical specialties (77.6%, additional information provided in Appendix 2) with a median number of licensed beds of 16 (IQR: 12.0–20.25). While a variety of ICU staffing models were reported, a minority (38.2%) mandated critical care consultation or management (i.e., the majority were not 'closed' ICUs).

Characteristics of patients receiving QT-interval prolonging drugs

Of 212,016 patients comprising the entire dataset, we identified 6,125 individuals (2.9%) receiving QT-interval prolonging drugs for duration of ≥24 hours (Table 2). While the admitting diagnostic categories of cardiovascular (12.0%), respiratory (17.2%), sepsis (8.2%), and trauma (4.1%) constituted the most common reasons for ICU admission, all admitting diagnostic categories captured by *Project Impact* were represented (Appendix 3). These individuals had a mean (±SE) age of 63.0 (±0.2) years, and were predominately male (55.4%) and Caucasian (84.4%). A minority of individuals had pre-existing disease, with cardiovascular (13.2%) and respiratory (10.2%) morbidity being most prevalent. Overall,

patients were exposed to QT-interval prolonging agents for a mean (±SE) 53.1 (±0.4) % of their ICU length of stay. ICU readmissions accounted for 13.5% of the patients in this study.

Co-administration of QT-interval prolonging drugs was observed in 1139 patients (18.6% of all patients receiving QT-prolonging agents). Compared to those receiving QT-interval prolonging agents individually, co-administration was associated with a greater ICU mortality rate and longer ICU length of stay ($p<0.001$ for both). Similarly, compared to those receiving QT-interval prolonging agents individually, patients receiving coadministered drugs were more likely to be male, and to have lower prevalence of pre-existing cardiovascular disease ($p=0.004$) (Table 2).

Pattern of QT-interval prolonging drug use in critically ill patients

The most commonly administered QT-interval prolonging drugs were Amiodarone (accounting for 23.5% of patients receiving these agents and administered a mean (±SE) 4.6 (±0.20) days), Haloperidol (19.8%, 3.3 (±0.1) days), and Levofloxacin (19.7%, 3.4 (±0.1) days). No other single agent analyzed accounted for greater than 10% of QT-interval prolonging drugs administered in our study (Figure 1). For our analysis, drugs were classified according to reported risk of inducing QT interval prolongation and *torsades de pointes*. A designation of '1' corresponds to a generally accepted risk of causing *torsades de pointes* while a designation of '2' denotes reported association with torsades de pointes but for which substantial evidence is lacking(4). With the exception of amiodarone, haloperidol, and erythromycin, most drugs administered to critically ill patients in our analysis in appreciable numbers carry a '2' designation.

Because the effect of QT-interval prolonging drugs on risk of *torsades de pointes* might be potentiated when these agents are simultaneously administered with agents having comparable effect, we examined frequency and patterns of QT-interval prolonging drug coadministration. QT-interval prolonging drugs most commonly coadministered with other QT-interval prolonging agents were Respiradone (62.9% of these patients received other QT-interval prolonging agents concomitantly, mean (±SE) duration of overlap 2.48 (±0.31) days), Moxifloxacin (50.5%, 3.04 (±0.29) days) and Erythromycin (33.5%, 3.30 (±0.32) days) (Figure 2). Patterns of QT-interval prolonging drug coadministration are presented in Table 3. Amiodarone coadministration with antibiotics (i.e., levofloxacin, azithromycin, gatifloxacin, erythromycin, moxifloxacin) comprised 15.2% of all coadministered drugs (2.7 (±0.2) days), haloperidol coadministration with antibiotics comprised 13.7% of all coadministered drugs (mean duration of coadministration 2.3 (±0.1) days), and haloperidol coadministration with amiodarone comprised 9.4% of all coadministered drugs (2.7 (±0.3) days). For patients receiving coadministered QT-interval prolonging drugs, overlap occurred for 71.4 (±0.8) % of the time that the drugs were given. As noted above, both amiodarone and haloperidol carry a '1' designation with respect to risk of association with *torsades de pointes*. Thus, the most frequent drug coadministration patterns in this population of critically patients involves at least 1 drug generally accepted as being associated with drug-induced QT-interval prolongation.

Discussion

Our purpose in performing this study was to profile QT-interval prolonging drug use in the ICU environment. We queried a large geographically and institutionally diverse critical care database to ascertain use of drugs associated with QT-interval prolongation and *torsades de pointes*. We found that approximately 3% of the individuals in our dataset received QT-interval prolonging drugs for at least 24 hours. These individuals represented a clinically heterogeneous group and were exposed to these agents on average for over one-half of their ICU lengths of stay. The majority of agents involved carry a '2' designation, i.e., they have

been associated with QT-prolongation and/or *torsades de pointes* but evidence supporting a causal link is lacking. Thus the risk posed by these agents is uncertain(4). We also examined frequency and patterns of QT-interval prolonging drug coadministration. This practice occurred in approximately 20% of individuals received QT-interval prolonging drugs. Compared to patients receiving these drugs individually, patients receiving coadministered agents had longer ICU lengths of stay and higher mortality rates, reflecting the complexity of their underlying illness. The most frequent drug coadministration patterns involved an agent with a '1' designation, i.e., generally accepted as having a risk of causing *torsades de pointes* (4).

Important differences emerge in comparing patterns of QT-interval prolonging drug use in ambulatory and critically ill patient populations. Curtis *et al* found that nearly one-fourth of ambulatory patients were prescribed QT-interval prolonging drugs, most commonly clarithromycin and erythromycin(2). In contrast, in addition to identifying a much small fraction of our critically ill patient population receiving these drugs, we found that haloperidol and amiodarone were the agents most commonly prescribed. Further, it appears that coadministration of QT-interval prolonging drugs occurs approximately one-half as frequently in ambulatory individuals than in critically ill patients(2). In addition, we found that many agents commonly used in ambulatory patients (e.g., fluoxetine, sertraline, amitriptyline) are rarely prescribed in the critical care setting(2). Finally, duration of drug administration in ambulatory patients exceeded what we found for critically ill individuals. Curtis *et al* defined drug coadministration as overlapping prescription of at least 7 days(2). In contrast, we identified no agent in which mean duration of administration exceeded 7 days, or in which mean duration of coadministration exceeded 3 days. How differences in pattern of drug administration, particularly more brief duration of exposure, might affect risk of adverse cardiac effect in critically ill compared to non-critically ill patients is unclear.

Our study has notable limitations. While interested in understanding the relationship between QT-prolonging drug exposure and adverse cardiac events in the setting of critical illness, our analysis is entirely descriptive. *Project Impact* does not capture electrocardiographic data, thus precluding us from determining whether exposure to these agents was associated with increased risk of *torsades de pointes*, or QT interval lengthening. Further, while able to analyze drug use patterns, we did not have information as to other factors potentially influencing arrhythmia predisposition, such as organ dysfunction, electrolyte abnormality, pharmacokinetic data, or presence of congestive failure or cardiac ischemia(1;3;5;7). This and other information will be necessary to accurately gage whether QT-interval prolonging drugs pose substantial risk in acute illness(22;23). An additional limitation is that our study may underestimate QT-interval drug use in this population. We limited our analysis to individuals receiving QT-interval prolonging drugs (either alone or in combination) for no less than 24 hours because we felt that this exposure represented the minimal clinical risk that we felt was sufficiently important to detect. Nonetheless, individuals receiving briefer exposure to these agents were excluded. Finally, while *Project Impact* has been used by prior researchers as an investigative tool, there are inherent limitations to using administrative databases for research purposes(16;18–20). Institutions participating in *Project Impact* are self-selecting and may not be representative of the broad population of intensive care units(18). Likewise, while a quality assurance audit of *Project Impact* supports its accuracy, data fidelity is a concern of observational databases(24). Specifically, inaccurate or non-randomly distributed missing data elements may bias our findings.

The above limitations not withstanding, our findings illustrate the potential challenges of determining whether QT-prolonging drugs are associated with adverse effect in the ICU setting. Amiodarone, the most frequently administered agent in our analysis, is prescribed

for arrhythmia suppression(25). Discerning whether amiodarone contributes substantially to arrhythmiagenesis in this context - and identifying safer therapeutic alternatives - may be problematic(25). Such concerns would not exist for many of the other QT-prolonging agents commonly administered to critically ill patients (antibiotics, anticonvulsants, and antipsychotics) that do not have cardiac disease as their primary indication. Nonetheless, given the small minority of patients we identified as receiving agents implicated in producing *torsades de pointes*, performing a sufficiently powered prospective study to demonstrate a causal effect may prove daunting(26).

Conclusion

It is becoming increasingly appreciated that pharmacoepidemiological studies are essential to detecting adverse drug effects not apparent in clinical trials conducted for purposes of regulatory approval(27–29). Such studies may acquire substantial importance in the domain of critical illness given that most pharmaceuticals haven't been thoroughly studied in this population, that these agents are frequently used for off-label indications, and that high baseline rates of morbidity and mortality potentially obscure drug-associated toxicity(30–32). QT-interval prolonging drugs appear to be used with less frequency and shorter duration in critically ill patients relative to ambulatory individuals. However, acutely ill patients frequently receive these agents in conjunction with drugs having comparable electrophysiological effects. Whether drug toxicities are less or more pronounced in critically ill relative to non-critically ill patients is unknown. Prospective evaluation - including collection of detailed pharmokinetic and electrocardiographic data - is necessary both to determine whether use of QT-interval prolonging drugs in the ICU setting is associated with adverse cardiac events, and to understand how the risk of such events might be mitigated.

BULLET POINTS:

- QT-interval prolonging drug use has not been systematically evaluated in the context of critical illness.
- Relative to use reported in ambulatory populations, QT-interval prolonging drugs appear to be administered less frequently and for shorter durations in critically ill individuals.
- Patients in whom QT-interval prolonging drugs are coadministered appear to be more severely ill compared to patients in whom these drugs are administered individually.
- Prospective evaluation is necessary to determine whether the use of QT-interval prolonging agents in the ICU setting is associated with adverse cardiac events.

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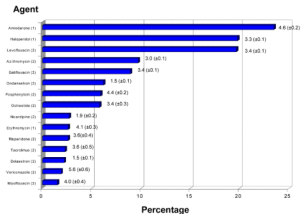


Figure 1. Administration of QT-interval prolonging drugs in critical illness

Frequency of QT-interval prolonging drug administration (as percentage of all QT-interval prolonging drugs administered) with associated mean (±SE) duration (days). Analysis was limited to drugs comprising at least 1% of all QT-interval prolonging drugs prescribed. Numbers in parentheses adjacent to drug names refer to the categorization with respect to risk of drug associated arrhythmia. As noted in Table 1, a designation of '*1*' denotes generally accepted to have a risk of causing *torsades de pointes* while '*2*' denotes reported association with *torsades de pointes* but for which substantial evidence is lacking(4). As this figure illustrates, with the exception of amiodarone, haloperidol, and erythromycin, most drugs administered to critically ill patients carry a designation of '*2*'.

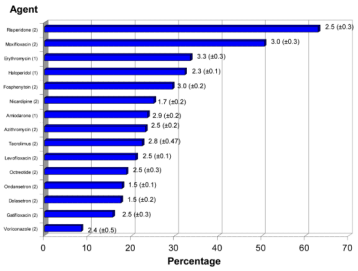


Figure 2. Frequency of Coadministration of QT-interval prolonging drugs

Frequency of QT-interval prolonging drug coadministration is illustrated (as a percentage of all patients receiving the individual agent) with duration of coadministration (mean (±SE) days). Drug designations are as noted in Table 1 and Figure 1.

Table 1

Drugs associated with QT prolongation/Torsade de pointes grouped according to major class[1]

Anti-infective		Antipsychotic/psychiatric		Cardiovascular		Miscellaneous	
Amantadine (2)	antiviral	Chlorpromazine (1)	antipsychotic	Amiodarone (1)	antiarrhythmic	Alfuzosin (2)	alpha1-antagonist
Azithromycin (2)	macrolide	Clozapine (2)		Bepridil (1)	CCA[2]	Arsenic trioxide (1)	anti-neoplastic
Clarithromycin (1)		Droperidol (1)		Disopyramide (1)	antiarrhythmic	Chloral hydrate (2)	Sedative
Erythromycin (1)		Haloperidol (1)		Dofetilide (1)		Felbamate (2)	antiepileptic
Foscarnet (2)	antiviral	Lithium (2)	mood stabilizing	Flecainide (2)		Fosphenytoin (2)	antiepileptic
Gatifloxacin (2)	quinolone	Mesoridazone (1)	antipsychotic	Ibutilide (1)		Indapamide (2)	diuretic (thiazide)
Gemifloxacin (2)		Paliperidone (2)		Isradipine (2)	CCA[2]	Levomethadyl (1)	opiate agonist
Halofantrine (1)	anti-malarial	Pimozide (1)		Moexipril/HCTZ (2)	anti-hypertensive	Methadone (1)	opiate agonist
Hydroxychloroquine (1)	anti-protazoal	Quetiapine (2)		Nicardipine (2)	CCA[2]	Octreotide (2)	somatostatin analogue
Levofloxacin (2)	quinolone	Risperidone (2)		Procainamide (1)	antiarrhythmic	Perflutren liquid microspheres (2)	Cardiac echo contrast agent
Moxifloxacin (2)		Thioridazine (1)		Qunidine (1)			
Ofloxacin (2)		Venlafaxine (1)	antidepressant	Ranolazine (2)		Tacrolimus (2)	immunosuppressant
Pentamidine (1)	anti-protazoal	Ziprasidone (2)	antipsychotic	Sotalol (1)		Tamoxifen (2)	estrogen antagonist
Sparfloxacin (1)	quinolone					Tizanidine (2)	alpha2-agonist
Telithromycin (2)	ketolide	Anti-emetics				Salmeterol (2)	beta2-adrenergic agonist
Voriconazole (2)	triazole	Dolasetron (2)	serotonin			Sunitinib (2)	anti-neoplastic
		Granisetron (2)	receptor			Vardenafil (2)	phosphodiesterase inhibitor
		Odansetron (2)	antagonist				

[1] Numbers in parentheses correspond to likelihood that the agent is associated with torsade de pointes according to the *Center for Therapeutics and Research (CERT)* (4) (accessed April 2008). A ranking of '1' denotes drugs that are generally accepted to have a risk of causing torsades de pointes while '2' denotes drugs that have reported association with torsades de pointes but for which substantial evidence is lacking. Drugs not availible in the US (i.e., astemizole, cisapride, domperidone, probucol, roxythromycin, terfenadine) are excluded.

[2] CCA - Calcium channel antagonist

Table 2

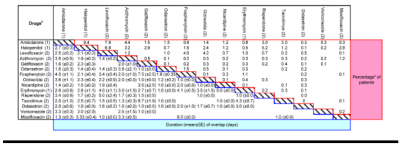
Characteristics of patients receiving QT-prolonging drugs

	All patients (n=6125)	QT-prolonging drugs not coadministered (n=4986)	QT-prolonging drugs coadministered (n=1139)	*p*-value[1]
Age (years) (±SE)	63.0 (±0.2)	62.8 (±0.20)	63.5 (±0.5)	0.474
Gender (% male)	55.4	54.5	59.2	0.005
Ethnicity (%)				0.955
Caucasian	84.4	84.2	85.4	
African American	8.3	8.4	8.0	
Latin/Hispanic	4.5	4.6	4.3	
Not specified/Other	2.7	2.8	2.3	
ICU Mortality Rate (%)	11.8	10.9	16.0	<0.001
ICU LOS (days) (mean±SE)	8.4 (±0.1)	7.2 (±0.12)	13.3 (±0.4)	<0.001
Pre-existing disease (%)				
Cardiac	13.2	13.8	10.5	0.004
Respiratory	10.2	10.1	10.7	0.610
Renal	3.2	3.3	2.5	0.195
Gastrointestinal	3.8	3.8	3.8	0.998

[1] Refers to comparison between patients not receiving and receiving coadministered QT-prolonging drugs

Table 3

Frequency (%) and duration (mean±SE) (days) of most commonly coadministered QT-prolonging drugs[1]



[1] Percentage represents number of patients receiving specified drug combination relative to all patients receiving coadministered QT-prolonging drugs

[2] Numbers in parentheses refer to risk of drug associated torsade de pointes as detailed in Table 1.

Appendix 1

Hospital Characteristics

Characteristic	Number of hospitals (%)	Number of patients (%)
American Hospital Association (AHA) region		
New England	7 (11.5)	1066 (17.4)
Mid-Atlantic	4 (6.5)	770 (12.6)
South Atlantic	11 (18.0)	1231 (20.1)
East North Central	15 (24.6)	1203 (19.6)
East South Central	1 (1.6)	61 (1.0)
West North Central	8 (13.1)	587 (9.6)
West South Central	4 (6.6)	388 (6.3)
Mountain	5 (8.2)	47 (0.8)
West	4 (6.6)	332 (5.4)
Not specified	2 (3.3)	440 (7.2)
Hospital classification		
Urban	33 (54.1)	3992 (65.1)
Suburban	19 (31.1)	1313 (21.4)
Rural	11 (18.0)	881 (14.1)
Organizational designation		
City/County	3 (4.9)	429 (7.0)
State	1 (1.6)	61 (1.0)
Community, For Profit, Non-Academic	4 (6.6)	53 (0.9)
Community, Not For Profit, Non-Academic	42 (68.8)	3348 (54.7)
Academic (University based)	14 (22.9)	2282 (37.2)

Appendix 2

Intensive Care Unit (ICU) specialty designations

Designation[1]	Number of ICUs (%)	Number of patients (%)
MICU/SICU combined	20 (26.3)	2363 (38.6)
MICU/SICU/CCU combined	16 (21.0)	1346 (22.0)
Other mixed medical, surgical/surgical subspecialty combined	13 (17.1)	415 (6.8)
MICU	8 (10.5)	97 (1.6)
Surgical/Trauma ICU	5 (6.6)	851 (13.9)
SICU	5 (6.6)	365 (6.0)
MICU/CCU combined	3 (3.9)	164 (2.7)
Trauma ICU	3 (3.9)	105 (1.7)
Cardiothoracic surgery	2 (2.6)	428 (7.0)
CCU	1 (1.3)	17 (0.3)
Other surgical/surgical subspecialty ICU combined	2 (2.6)	20 (0.3)

[1] MICU - Medical ICU; SICU -Surgical ICU; CCU -Coronary Care Unit.

Appendix 3

Distribution of patients by admitting diagnostic category

Admitting diagnosis category	Number (%)
Cardiovascular	738 (12.0)
Respiratory Infection	531 (8.7)
Respiratory (not otherwise specified)	525 (8.6)
Sepsis	501 (8.2)
Multiple Trauma	252 (4.1)
Gastrointestinal Bleeding	248 (4.0)
Chronic Obstructive Pulmonary Disease	235 (3.8)
Gastrointestinal (not otherwise specified)	232 (3.8)
Congestive Heart Failure	221 (3.6)
Heart Valve Surgery	209 (3.4)
Intracerebral hemorrhage	208 (3.4)
Post-Cardiac Arrest	205 (3.3)
Neurologic (not otherwise specified)	178 (3.9)
Coronary Artery Disease	171 (2.8)
Respiratory Insufficiency after Surgery	160 (2.6)
Post-Respiratory Arrest	154 (2.5)
Metabolic/Renal (not otherwise specified)	132 (2.1)
Gastrointestinal Perforation/Obstruction	122 (2.0)
Peripheral Vascular Surgery	109 (1.8)
Gastrointestinal Surgery for Neoplasm (any type)	97 (1.6)
Aspiration/poisoning/toxic exposure	96 (1.6)
Rhythm disturbance	96 (1.6)
Craniotomy for Intracerebral hemorrhage	74 (1.2)
Hemorrhagic Shock/Hypovolemia	70 (1.1)
Head Trauma (confined to the head)	68 (1.1)
Seizure Disorder	61 (1.0)
Craniotomy for neoplasm	59 (1.0)
Drug Overdose	54 (0.9)
Thoracic Surgery for Neoplasm	33 (0.5)
Asthma/allergy	32 (0.5)
Pulmonary Edema (non-cardiogenic)	32 (0.5)
Pulmonary Embolus	32 (0.5)
Cardiogenic Shock	29 (0.5)
Laminectomy and Other Spinal Cord Surgery	27 (0.4)
Diabetic Ketoacidosis	25 (0.4)
Respiratory Neoplasm	23 (0.4)
Chronic Cardiovascular Disease	23 (0.4)
Hypertension (hypertensive crisis)	21 (0.3)
Dissecting Thoracic/Abdominal Aneurysm	16 (0.3)

Admitting diagnosis category	Number (%)
Renal Transplant	15 (0.2)
Renal Surgery for Neoplasm	11 (0.2)