The Role of Excess Weight in Antibiotic Treatment Failure

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ABSTRACT

Objectives: To determine whether excess weight is associated with antibiotic treatment failure (ATF) and if this may be due to a lack of weight-based dosing.

Methods: Using a historical cohort study design, data linked to Quebec administrative databases were available for 18 014 consenting patients randomly sampled from the 1992 and 1998 Santé Québec Health surveys (response rate 85%). Selected patients were within the normal weight, overweight and obese weight classes aged 20–79 years, receiving at least one episode of antibiotic therapy from the health survey date to December 2005. ATF was measured via secondary antibiotic prescriptions or additional hospitalizations for infections within the month following initial therapy for each participant. The antibiotic daily dose (DD) and daily dose to body mass index (DD:BMI) ratios were computed for those receiving an oral antibiotic prescription. Logistic regression was performed to determine whether overweight and/or obesity as well as dosing factors (e.g. DD:BMI) were significant predictors of ATF, while one-way ANOVA with Tukey-Kramer adjustment for multiple comparisons was used to determine if DD:BMI ratios differed significantly across weight groups, reflecting a lack of weight-based dosing.

Results: Of the 6 179 patients selected, 828 (13.4%) had an ATF event during the outcome assessment period. Obesity was found to be a significant predictor of ATF with an OR of 1.26 (95% CI 1.03-1.52), after adjusting for other potential confounders including sociodemographic, and antibiotic-related factors (e.g. MRSA and history of antibiotic use). The antibiotic DD:BMI ratio means differed significantly between weight groups, where means decreased with increasing BMI. When included in the ATF predictive model along with other previous confounding factors, the DD:BMI variable was significant (p-value of 0.03) with a modest adjusted OR of 1.004 (95% CI 1.000-1.007).

Conclusions: Obesity is a significant predictor of ATF and this association is likely due to the current "one size fits all" dosing strategy. Findings may encourage further research in the field of pharmacokinetics and family medicine

to find a means of standardizing current antibiotic dosing guidelines for weight as well as implementing weight-based dosing in family practice.

RÉSUMÉ

Objectifs: Déterminer s'il existe un lien entre le surpoids et l'échec d'un traitement antibiotique (ÉTA) et si le fait de ne pas régler la dose en fonction du poids peut en être la cause.

Méthodes: À partir d'une étude historique de cohorte, nous avons utilisé un échantillon aléatoire de 18 014 patients consentants tiré des enquêtes de Santé Québec entre 1992 et 1998 (taux de réponse de 85%). Parmi les patients sélectionnés, on retrouvait des groupes de personnes de poids normal, faisant de l'embonpoint et souffrant d'obésité avec un écart d'âge variant de 20 à 79 ans et ayant reçu au moins un traitement antibiotique entre le début de l'enquête et décembre 2005. Pour mesurer l'ÉTA, nous avons noté les répétitions de prescriptions d'antibiotiques ou les hospitalisations supplémentaires à cause d'infections au cours du mois suivant le traitement initial de chaque participant. Les ratios de la dose quotidienne (DQ) d'antibiotiques et de la dose quotidienne par rapport à l'indice de masse corporelle (DQ:IMC) ont été calculés pour les personnes avec une prescription d'antibiotiques oraux. La régression logistique à été utilisée pour déterminer si le surpoids et/ou l'obésité ainsi que d'autres facteurs de dose (ex. le ratio DQ:IMC) constituaient des variables prédictives pour l'ÉTA. Par ailleurs, l'ANOVA avec l'ajustement pour comparaisons multiples de Tukey-Kramer ont été utilisés pour déterminer si les ratios DQ:IMC variaient de façon significative d'un groupe à l'autre, ce qui signalerait l'absence de dosage en fonction du poids.

Résultats : Parmi les 6 179 patients sélectionnés, 828 (13.4%) avaient subi un ÉTA durant la période d'évaluation. Les résultats ont révélé que l'obésité constituait un facteur significatif de l'ÉTA avec un rapport de cote (RC) de 1.26 (95% IC 1.03-1.52), ceci après avoir ajusté les données en fonction des variables de contrôles possibles comme les variables sociodémographiques ou les facteurs reliés aux antibiotiques (ex. le SARM et les antécédents d'utilisation d'antibiotiques). Les moyennes du ratio DQ:ICM variaient de façon significative d'un groupe à l'autre, alors que les moyennes diminuaient quand l'ICM augmentait. Lorsqu'on l'inclut dans le modèle prédictif de l'ÉTA avec d'autres

variables précédents, la variation du ratio DQ:ICM était significative (valeur p de 0.03) avec un RC ajusté de 1.004 (95% IC 1.000-1.007).

Conclusions : L'obésité constitue un facteur prédictif significatif de l'ÉTA. Cette association est probablement reliée au fait que les doses sont administrées uniformément parmi les différents groupes de poids. Ces découvertes devraient encourager d'autres recherches dans le domaine de la pharmacocinétique et de la médecine familiale, afin de pouvoir établir des normes de dosage des antibiotiques axées sur le poids et d'intégrer dans la pratique médicale courante l'administration de doses en fonction du poids.

GLOSSARY OF PHARMACOLOGY TERMS

Pharmacokinetics/Pharmacodynamics: Key Parameters, Measures and Dosing Terms

AUC

The AUC (i.e. the area under the curve) is a pharmacodynamic index referring to the area under the plasma drug concentration vs. time plot following antibacterial administration. The AUC is of particular use when determining the bioavailability and total clearance or exposure profile of antibiotic medications.[1] The figure below depicts the AUC on the concentration vs. time plot along with other pharmacokinetic parameters Cmax and MIC defined below.[2]

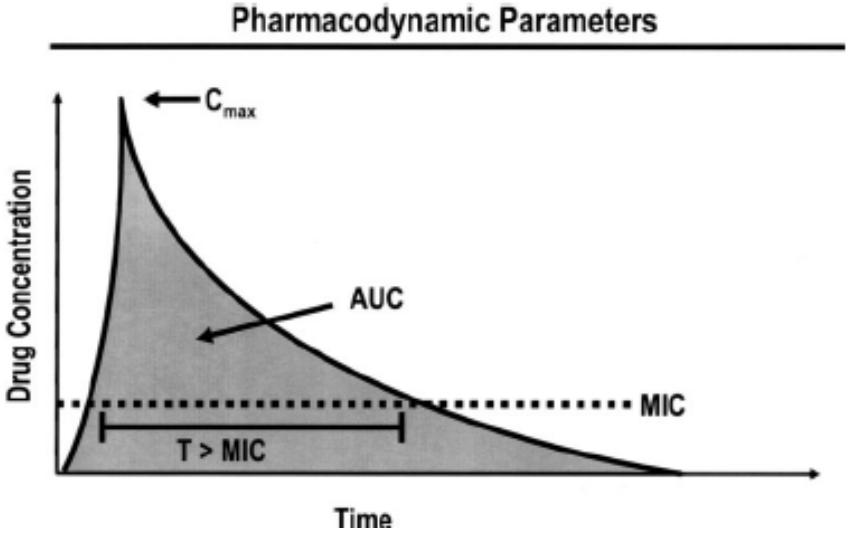


Figure Source: Crit Care Med © 2005 Lippincott Williams & Wilkins

Bioavailability

Antibacterial drug bioavailability refers to the proportion of medication successfully absorbed into the blood following extravascular administration. Various antibiotics have similar bioavailability and oral absorption rates to intravenous formulations in healthy subjects, while others such as β-lactams are only partially absorbed as they first go through hepatic metabolism prior to reaching the systemic circulation.[3]

Cmax ('Peak' Concentration) and Cmin ('Trough' Concentration)

The Cmax is defined as the observed maximum or peak concentration of an antibiotic medication after it has been administered. Accordingly, the Cmin is defined as the observed minimum or trough concentration after consumption and/or just preceding a subsequent dose.[1]

Clearance (CL)

The clearance of an antibacterial medication is defined as "the volume of blood from which the drug is completely removed in a given allotment of time" and is largely dependent on patient physiology. Therefore, the CL of an antibiotic medications will be a function of the blood flow to that specific organ as well as its ability to efficiently remove the drug from the blood.[4] Antibiotic medications are metabolized in the liver and eliminated via the renal or non-renal (gastrointestinal) clearance pathways.[5] The CL parameter of the antibacterial determines a patient's maintenance dose regimen.[4]

Elimination Half-Life ($t_{1/2}$), Minimal Effective & Steady State Concentrations

The minimum effective concentration, or the MEC, is defined as the minimum required antibacterial drug concentration in the blood to exert its desired effect. The MEC is often used interchangeably with the MIC; however, they are distinguishable in that the MEC is as an *in vivo* parameter, while the MIC is an *in vitro* parameter. The steady state concentration refers to the point where the balance of antibiotic drug absorption and distribution with metabolism and elimination reaches equilibrium. The half-life of antibacterial medications is defined as the time needed for the removal of 50% of the drug concentration from the blood and represents the agent's rate of clearance from the body. This determines when a steady-state concentration can be reached.[5]

Loading and Maintenance Doses

The first of a series of antibiotic doses administered to the patient in a multiple-dose regimen is referred to as the loading dose. It is given as a larger

than average dose as a means of achieving the required therapeutic concentrations more rapidly in the body to successfully begin the eradication of suspected bacterial microorganisms. On the other hand, maintenance doses are all other doses subsequent to and smaller than the initial loading dose functioning to maintain drug concentrations at the desired levels.[1]

Volume of Distribution (Vd)

The volume of distribution of antibacterial medications refers to a hypothetical volume of drug that has the ability to uniformly disperse in tissue as well as in the bloodstream.[5] In other words, Vd predicts the extent to which antibiotics distribute into extravascular tissues. Accordingly, antibiotics that distribute extensively into tissues generally have larger Vd values. Distribution into tissue depends on several drug-related physiochemical factors such as molecular size, degree of ionization, lipophilicity and ability of the antibiotic to cross membranes.[4] For instance, lipophilic antibacterials have increased uptake into adipose tissue leading to a change in the Vd parameter in obese individuals.[6] However, blood flow to the tissues as well as plasma protein binding may also modify Vd; increased binding to serum protein can disrupt the activity of antibacterial medications, since only unbound drug has the ability to exert the desired pharmacological effects.[7] Pharmacokinetic studies are necessary in evaluating the Vd parameter in different patient populations, specifically in obesity, as this is the principal factor of interest for determining the antibacterial loading-dose (i.e. the initial higher dose of a drug given at the beginning of a course of treatment).[4]

Weight Measures and Definitions in Pharmacokinetics

According to the Center of Disease Control and Prevention, excess weight is defined as being either overweight or obese, where both are labels given to the ranges of weight estimated as greater than what is generally considered to be healthy, for a given height.[8] Although direct measures of body composition are ideal to approximate body fat, most quantitative methodologies (e.g. underwater

weighing, skinfold measurement, bioelectrical impedance analysis) are not readily available to the majority of clinicians.[4] Thus, indirect measures of body composition are commonly used to classify individuals with excess weight in pharmacokinetic studies.

(1) Body Mass Index (BMI)

Body mass index is calculated as total bodyweight (TBW) in kilograms divided by the square of the height in meters. An adult is considered to be within the normal weight category if his/her BMI falls in the 18.5kg/m^2 to 24.9kg/m^2 range, and overweight or obese categories if he/she has a BMI within the 25 kg/m^2 to 29.9 kg/m^2 or $\geq$ 30 kg/m^2 range, respectively.[9] This definition is in agreement with that of the WHO described in 2006.[10,11] Although body mass index is the international metric that defines each of the weight categories, its use does not come without limitations. The failure to distinguish between adipose tissue and lean muscle mass, which is of particular importance to athletes, as well as the fact that BMI is not gender specific may cause a small degree of misclassification between weight groups.[9] Nevertheless, the BMI classification system can be used to distinguish weight groups in pharmacokinetic studies.

(2) Ideal Body Weight (IBW) and Lean Body Weight (LBW)

Ideal body weight is often used as a means of approximating lean body weight (i.e. non-fat cell mass and intercellular connective tissue responsible for more than 90% of metabolic activity). Using the Devine formula (see below), IBW is calculated based on body weight, height and sex.[12] Similarly, obesity may also be defined as $\geq$125% IBW, while 80-124% IBW would be considered normal weight.[13] These definitions are most common in pharmacokinetic studies as a means of comparing drug disposition parameters (Vd, CL, $t_{1/2}$ etc.) between normal and obese weight groups.

Devine Formula[12]

IBW for Males = 50 kg + 2.3 kg/inch for height over 5 feet
IBW for Females = 45.5 kg + 2.3 kg/inch for height over 5 feet

1.0 INTRODUCTION

1.1 BACKGROUND

1.1.1 Overview of the Health Problem: Obesity, Infection and Primary Care

Obesity is a growing epidemic and is considered to be one of the world's most prevalent health problems according to the World Health Organization (WHO).[14] Of the 1.6 billion people classified as overweight worldwide, at least 400 million (25%) are obese.[15] Statistics Canada reports that approximately 60% of Canadian adults are overweight and an estimated 23% are obese.[16] Findings from the 2003 Santé du Québec population survey revealed that 840 000 (14%) of the 6 million people living in Quebec were obese.[17] The WHO defines overweight individuals as having a body mass index (BMI) of 25 kg/m^2 to 29.9 kg/m^2 and classifies obese individuals as having a BMI greater than or equal to $30kg/m^2$.[10,11] Mortality attributable to excess weight nearly doubled between 1985 and 2000. It was estimated that 1 in 10 premature deaths among Canadians aged 20-64 years may be directly accredited to excess weight.[18] Furthermore, various studies have indicated that obese persons have a higher likelihood of hospital admissions and length of stay as compared to normal weight persons.[19-29] The WHO reports that Canada spends between 2-2.4% of its total national expenditure on obesity-associated health problems, which translates to over $4.3 billion dollars of total health care costs.[14] With Canadian obesity rates projected to have risen to 27% for men and 24% for women in 2010, such costs will only inflate.[30]

As the obesity epidemic and associated health care costs continue to rise dramatically, the need for obesity-tailored patient care has now become an urgent issue in Canada, particularly in the primary health care setting. Family physicians (FPs) often serve as the first contact for obesity-related health problems and play a pivotal role in the prevention, early detection, treatment and management of obesity. In a typical practice, 60% of patients will be overweight and 26% will be obese.[16,17] Visits to primary care physicians have been reported to be approximately 38% higher in the obese patient demographic when compared to

normal weight individuals.[15] While obesity is a well-established risk factor for cardiovascular disease, hypertension, diabetes, liver disease and certain types of cancer,[15] it has recently been shown to compromise the immune response through a variety of immune mediators leaving its host highly susceptible to acquiring infection.[31] As a result, family physicians, who issue 70% to 80% of all prescriptions in Canada, are prescribing antibacterial medications more frequently to obese patients as compared to their normal weight counterparts.[32] This substantial increase in antibiotic prescribing among patients with excess weight has been previously described by the Counterweight Project Team.[33] Among the list of common indications for outpatient antibiotic prescription use, upper and lower respiratory tract infections, more specifically community acquired pneumonia, as well as soft tissue and skin infections, dominate in this patient demographic.[31, 34] In 2000, it was estimated that 1 million physician visits and 60 000 hospitalizations were the result of community-acquired pneumonia (CAP) in Canada annually, accounting for approximately $100 million dollars in health care service costs.[35] Accordingly, the compounded problem of obesity with an increased incidence of infection may burden Canada's health care system tremendously, which is now showing consistent signs of distress.

1.1.2 Obesity and Infection

The discovery of obesity as a risk factor for a variety of infections has caused a great deal of concern among physicians.[31, 36] With obesity rates increasing exponentially worldwide, the lack of guidelines specific to the management of infections in the obese patient population may lead to worse clinical outcomes, and perhaps even death.[31] In fact, a recent systematic literature review (2009) evaluating the effect of body mass index on the outcome of infections established that obesity was strongly associated with poorer clinical outcomes, defined as mortality in the hospital setting. The notion that current antibiotic dosing regimens are inadequate, since they are not adjusted for a patient's body weight, has been a hot topic of debate among researchers in the field of pharmacokinetics and is postulated to be responsible for therapeutic

failure in obese patients with infections. This hypothesis is supported by the fact that antibiotic medications have an altered drug disposition profile in individuals with excess weight, which ultimately affects their ability to attain therapeutic targets.[37]

Pharmacokinetic evidence suggests that excess body fat may increase the volume of distribution (i.e. hypothetical volume of drug that has the ability to uniformly disperse in tissue as well as in the bloodstream) and clearance (CL) of antibacterial medications. [6, 12, 38, 39] While the elevated systemic clearance rate has been reported to be due to adipose-related physiological changes of the renal and hepatic cells causing hyperactivity,[6, 40] the volume of distribution (Vd) drastically increases as antibiotics readily distribute into adipose tissue.[6] Consequently, this decreases the amount of unbound drug available for pharmacologic activity at the site of infection. Since the Vd and CL pharmacokinetic parameters determine antibiotic loading and maintenance doses, respectively, it has been suggested that obese individuals may benefit from larger initial doses as well as shorter dosing intervals as a means of better achieving therapeutic targets.[36] A comprehensive review of the pharmacokinetic literature concerning antibiotic dosing in the obese adult population revealed that the modifications in Vd and CL generally result in less than optimal drug concentrations in the blood and tissue for the most commonly prescribed antibiotic classes; however, the clinical consequences of suboptimal antibiotic concentrations as a direct result of dose inadequacy remain to be assessed.

In the primary health care setting, antibiotic treatment failure (ATF) is judged to have occurred if infection symptoms have not resolved following the completion of the course of oral antibacterial treatment. Reported ATF rates can reach up to 64%, a significant proportion of which are preventable.[41] Possible causes of ATF range from patient non-compliance of physician treatment instructions[42] to antibiotic-related variables such as insufficient coverage (i.e. narrow-spectrum vs. broad-spectrum antibacterial agents), inappropriate use against infections not of bacterial origin (i.e. viral infections), antibacterial resistance as well as unattained therapeutic targets due to inadequate antibiotic

dosage.[43] Among the list of potential reasons for ATF occurrence, only the risk of methicillin-resistant staphylococcus aureus (MRSA) acquisition and difficulty attaining therapeutic targets have been shown to differ between normal weight and excess weight patient groups; however, MRSA is not nearly as prevalent in primary care as it is in the hospital setting.[44] Therefore, one of the most probable reasons for higher rates of antibiotic failure in obese than in non-obese patients treated at the primary care level is that of unattained therapeutic targets resulting from insufficient antibiotic dosage.

Determining whether excess weight affects the occurrence of antibiotic treatment failure is highly clinically relevant. Oral antimicrobial dispensing rates as well as prescribing volumes are increasing across Canada, as reported by Public Health Agency of Canada in 2006.[45] Moreover, the elevation in the aforementioned prescribing variables has been found to be more pronounced in individuals with excess weight and tends to rise significantly with higher degrees of obesity.[33] The implications of ATF on obese patient outcomes can range from minor health complications such as the need for additional or secondary antibiotic prescriptions to major health complications such as hospitalizations or even death due to sepsis. Similarly, treatment failure is associated with significantly increased length of hospital stay, higher mortality rates and greater health care costs.[46] From an ecological perspective, ATF can also contribute to antibiotic resistance which further promotes the occurrence of treatment failure - a vicious cycle.[41]

1.2 STUDY OBJECTIVES

The primary objective of this study is to determine, among persons receiving antibiotic therapy, the extent to which being overweight or obese is associated with the occurrence of antibiotic treatment failure (ATF) as indicated by secondary antibiotic prescriptions or hospitalizations for infections in the month following initial therapy as compared to normal weight persons. The second objective is to determine whether a lack of weight-based antibiotic dosing is associated with the primary health outcome (ATF).

2.0 LITERATURE REVIEW

2.1 OBESITY AND INFECTION

2.1.1 Obesity and the Risk of Infection: Epidemiological Evidence

The association between increased risk of infection and excess weight has been fairly recently documented in the literature. In 2004, Christou and associates reported that in a cohort of almost 6 000 people with morbid obesity, approximately 62% were hospitalized for an infectious disease over a 5 year time frame.[47] Several clinical studies have revealed an increased incidence of upper and lower respiratory tract infections, community-acquired pneumonia (CAP), nosocomial and surgical-site infections, skin infections as well as ondontogenic infections in obese patients when compared to non-obese patients.[31] In a large population-based study consisting of 26 429 men from the Health Professionals Follow-up Study[48] and 78 062 women from the Nurses' Health Study II,[49] a direct relation between BMI and risk of CAP among women was observed. Similarly, women and men who gained weight (40 lbs or more) during adulthood had nearly a two-fold increase in relative risk for CAP as compared to those who maintained their weight (RR 1.71 for men; RR 2.13 for women).[50] Obesity has also been closely linked to a higher risk of aspiration in patients with obstructive sleep apnea as well as chronic inflammation of the upper and lower respiratory tract.[51-53] Accordingly, obesity is associated with an increased risk of aspiration pneumonia as compared with normal weight patients in the hospital setting.[54] With respect to nosocomial and post-operative surgical site infection risk, an abundance of evidence suggests that obese patients have a much higher probability of acquiring infection than non-obese patients.[54-66] Lilienfeld and associates found that the occurrence of wound and/or endocarditis infections in 20 of 1204 patients following coronary artery bypass grafting was six times more likely in obese as compared to non-obese persons (OR 6.2).[64] Although diabetes mellitus is a well known risk factor for post-operative infections, Harrington and colleagues demonstrated that obesity is an independent predictor of surgical-site

infections in patients following coronary artery bypass grafting (CABG) surgery; for 4 474 patients who underwent CABG surgery, the odds ratios (ORs) for surgical site-infection were 1.8 and 1.6 for the risk factors obesity and diabetes mellitus, respectively.[66] Furthermore, opportunistic skin infections such as intertrigo, candidiasis, furunculosis, erythrasma, tinea cruris and folliculitis occur frequently among obese patients, although cellulitis, necrotising facitis and gas gangrene are also encountered to a lesser extent.[67,68] Thorsteinsdotter and colleagues found that abdominal wall cellulitis is a unique infectious complication in patients with morbid obesity; of 312 patients with morbid obesity and soft tissue infection, 260 had primary abdominal wall cellulitis (83.3%).[67] The incidence of erysipelas, a serious infectious disease of the skin encountered mainly in the primary care setting, has also been reported to be high in obese individuals. In a nested case-control study using a primary care database in Belgium, obese patients aged 45 to 64 years were nearly four times more likely to have erysipelas than non-obese patients (45-64 yrs, OR 4.10; >64 yrs, OR 1.99).[69]

2.1.2 Physiological Mechanisms Predisposing Obese Patients to Infections

Despite an abundance of epidemiological evidence, researchers continue to investigate the underlying cellular pathways explaining the association between excess weight and higher infection risk. Several studies describe a variety of physiological mechanisms potentially responsible for predisposing obese patients to infection. Although quite complex, the mechanism consensus amongst immunologists seems to involve adipose-regulated hormone secretion;[31] however, the key adipose-derived cellular components responsible for modulating the inflammatory pathway remain to be clarified. Nevertheless, adipose tissue has been shown to actively participate in the immune response to infection via the production and release of various pro-inflammatory and anti-inflammatory factors such as the adipokines leptin and adiponectin.[70]

Leptin is a protein coded by the *ob* gene and exerts its primary physiological effect, the regulation of appetite, through specific cellular transduction pathways once attached to its respective leptin receptor, which is

coded by the *db* gene. Both the *ob* and *db* genes are postulated to be mutated in obese individuals.[71-73] After various early observations of thymus atrophy in leptin receptor deficient (*db/db*) mice, researchers began to investigate the role of leptin in regulating the host immune response to infection. It has been reported that leptin plays a protective role with respect to the T lymphocyte life-cycle, inhibiting apoptosis as well as regulating T-cell proliferation and activation. Moreover, leptin also stimulates T-lymphocyte cytokine production resulting in the T-cell switch to the T_H1 phenotype, further enhancing the cytotoxic capability of the pro-inflammatory response. In addition to promoting T lymphocyte survival and consequently the adaptive immune response, leptin also influences monocyte activation, phagocytosis and cytokine production, all of which contribute to protecting the host from infection.[74-76]

Adiponectin is a collagenous protein that has anti-inflammatory properties and mainly serves to inhibit interleukin 6 (IL-6) production, a protein involved in the host resistance to bacterium, as well as induce other anti-inflammatory cytokines such as interleukin 10 (IL-10) and interleukin 1 receptor antagonist (IL-1RA).[77-79] Furthermore, adiponectin also decreases the production and activity of tumor necrosis factor alpha (TNF-α), a potent inflammatory molecule that can stimulate the acute phase reaction as well as induce apoptotic cell death.[80] Nonetheless, studies reveal that obese subjects typically exhibit reduced adiponectin levels.[81]

The genetic defect of leptin-deficient *ob/ob* mice, shown to be the cause of a severe obese phenotype, is associated with increased susceptibility to bacterial and viral infections.[82-87] This is postulated to be mainly due to the impairment of phagocytic functions and reduced T-cell function. Farooqi and colleagues demonstrated that leptin-deficient children also have suppressed T-cell cytokine production.[88] Moreover, although reduced in obese individuals, adiponectin can continue to exert anti-inflammatory effects, further predisposing these individuals to infection. Other theories regarding increased susceptibility of obese patients to infection are less developed; evidence suggests that decreased arginine and glutamine bioavailability and reduced TNF-α production as well as elevated nitric

oxide levels may be related to an increased risk of infection, since it has been observed in obese rats.[89] Conversely, microvascular inflammation and thrombosis is hypothesized to be associated with sepsis-related morbidity in obese patients.[90]

Given that the same genetic predisposition (i.e. leptin deficiency) responsible for the obese phenotype is also hypothesized to be the primary cause of an increased susceptibility to infection, physicians face the additional challenge of managing infection in these patients who are otherwise considered to be in poor health, as co-morbidity often accompanies obesity. Accordingly, the lack of guidelines specific to the management of infections in the obese patient population may lead to worse clinical outcomes.

2.1.3 The Effect of Obesity on the Outcome of Infections

Despite the abundance of evidence demonstrating the strong associations between excess weight and infection risk, a paucity of studies have evaluated whether BMI affects the health outcome for infections and if this differs with respect to each weight group. In a recent systematic literature review (2009) concerning this topic,[37] mortality was found to be higher in obese as compared with non-obese patients for bacteraemia[91] (RR 9.8; 95% CI 2.3 to 41.3) as well as pneumonia[92] (both community and hospital-acquired). Moreover, mortality was also reported to be higher in morbidly obese patients as compared to non-morbid[93] and non-obese patients[94] with cellulitis (OR 5.19; 95% CI 1.53–17.64) as well as pneumonia or sepsis (RR 2.29), respectively. Overall, obesity was strongly linked to worse patient outcomes in four of the seven studies reporting relevant findings, while the opposite association (i.e. obesity linked to better patient health outcomes) was not observed in any of the included review studies. In speculating about the potential underlying causes of this association between BMI and worse infection outcomes, the authors suggested that current antibiotic dosing regimens are inappropriate as they are not adjusted for patients' body weight, which may cause therapeutic failure in obese patients with infections. This hypothesis is supported by the fact that antibiotic medications have an altered drug distribution

profile in individuals with excess weight, which may affect their ability to attain therapeutic targets.[37]

2.2 PRESCRIBING AND PHARMACOLOGY OF ANTIBIOTICS

2.2.1 Antibacterial Prescribing Patterns in Primary Care

In a retrospective descriptive study using the General Practice Research Database (GPRD), the world's largest primary care database of consultations and prescriptions, the top ten most frequently prescribed antibacterials in the UK between 1998 and 2001 were: 1) amoxicillin, 2) erythromycin, 3) flucloxacillin, 4) trimethoprim, 5) phenoxymethylpenicillin, 6) aminoglycoside, 7) chloramphenicol, 8) tetracycline, 9) co-amoxiclav, and 10) cefalexin. Accordingly, the top ten indications (in descending order) for antibacterial prescribing were: upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), sore throat, urinary tract infection (UTI), otitis media, conjunctivitis, vague skin infections, sinusitis, otitis externa, and impetigo. [34] The most commonly prescribed antibacterials for each indication are summarized in the table below.

Table 2.1–Top Indications and Antibiotics Prescribed in Primary Care, 1998-2001[34]

Table 2.1 The most common infection indications along with their corresponding antibacterials are described relative to the primary care setting in the United Kingdom using the GRPD database.

INDICATION	MOST COMMONLY PRESCRIBED ANTIBIOTICS	
1. URTI	Amoxicillin (58.6%)	Erythromycin (11.7%)
2. LRTI	Amoxicillin (56.5%)	Erythromycin (12.7%)
3. SORE THROAT	Penicillin (62.2%)	Amoxicillin (17.0%)
4. UTI	Trimethoprim (56.1%)	Cefalexin (14.2%)
5. OTITIS MEDIA	Amoxicillin (65.3%)	Erythromycin (9.7%)
6. CONJUNCTIVITIS	Chloramphenicol (65.4%)	Aminoglycoside (30.5%)
7. SKIN INFECTION	Flucloxacillin (39.9%)	Fusidic Acid (13.3%)
8. SINUSITIS	Amoxicillin (43.2%)	Tetracycline (31.2%)
9. OTITIS EXTERNA	Aminoglycoside (64.3%)	Amoxicillin (10.9%)
10. IMPETIGO	Flucloxacillin (38.4%)	Fusidic Acid (30.0%)

In Canada, the most recent report from the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) describes antimicrobial

consumption trends from 2000 to 2006.[45] The five most frequently dispensed oral antibiotic classes in descending order were: extended-spectrum penicillins, macrolides, tetracyclines, fluoroquinolones, and first generation cephalosporins. Significant increases in drug consumption during the course of surveillance were observed for fluoroquinolones, extended-spectrum penicillins, first generation cephalosporins, macrolides (although the consumption of erythromycin had decreased considerably), lincosamides, and nitrofuran derivatives. In 2006, antimicrobial consumption was the highest in the provinces of Prince Edward Island and Newfoundland, while Quebec ranked the lowest with regard to overall antimicrobial consumption rates. [45]

Antibacterial prescribing variables in primary care specific to the obese patient population were also reported by the Counterweight Project Team;[33] the WHO total defined daily doses (DDDs) of medications (i.e. the assumed average maintenance dose per day for a drug used for its main indication in adults)[95] for each prescribing category as well as the total number of patients dispensed at least one drug during the course of 18 months were evaluated for the obese and normal weight groups. An increased number of patients receiving antibiotic medications as well as significantly higher prescribing volumes (i.e. total DDDs) for the obese as compared to the normal weight groups were reported (ratio of prescribing volume of 1.2 for obese vs. normal weight). Additionally, findings revealed that prescribing rates were higher with increasing degrees of obesity after adjusting for potential confounders.[33] Since obese individuals have a higher susceptibility to infection, potential explanations for higher prescribing rates and prescribing volumes in obesity include increased incidences of multiple infections and/or the need for higher daily doses in order to successfully attain therapeutic targets, respectively. The latter explanation presents an interesting case as pharmacokinetic evidence suggests that the efficacy of antibiotic medications may decrease in obese patients as a result of the modifications in drug distribution parameters that typically accompany large increases in adipose tissue.[4] The following sections will cover the pharmacology of antibacterial medications in detail with respect to the obese patient population.

2.2.2 Pharmacodynamics: Predictors of Antibacterial Efficacy

Pharmacodynamics is the field of study relating to the pharmacologic effects exerted by particular medications on the human body, which includes the beneficial and adverse outcomes of drug consumption.[5] The pharmacodynamic profiles of antibacterial agents can be generally classified into two distinct categories: bactericidal and bacteriostatic drugs. Antibacterial agents that are capable of killing microorganisms are termed "bactericidal," while those that exert their pharmacologic effect through inhibiting bacterial growth are known as "bacteriostatic."[5] Nevertheless, clinical or eradication success for both antibacterial classes is dependent on sufficient concentrations at the site of infection as well as the maintenance of these concentrations for an adequate time frame.[96]"Sufficient concentrations" in this context refers to drug levels exceeding the minimal inhibitory concentration or the MIC of the susceptible pathogen, which is defined as the lowest concentration of an antibiotic medication that will inhibit the visible growth of the bacterium in vitro.[5] The minimal effective concentration, or the MEC, is similar to the MIC; however, the former is an *in vivo* parameter, while the latter refers to an *in vitro* concentration. Accordingly, an antibiotic medication must achieve its cutoff MEC *in vivo* to attain the therapeutic targets necessary for clinical success.[i]

2.2.3 Impact of Excess Weight on the Attainment of Therapeutic Targets

2.2.3.1 Modifications in Antibacterial Pharmacokinetics in Patients with Excess Weight

Pharmacokinetics (PKs) is the study of the absorption, distribution, metabolism and elimination of medications. The bioavailability, volume of distribution, clearance, elimination half-life ($t_{1/2}$), achieved minimal effective and steady-state concentrations of medications are central parameters when discussing antibiotic treatment effectiveness.[5,97] Refer to the glossary found in the preface for

[i] Appendix 1 contains further information on antibacterial efficacy as well as the key characteristics and mode of activity for the most commonly prescribed antibiotic medications in primary care.

further explanation of common pharmacology terms and/or further details concerning the key pharmacokinetic parameters and measures of interest.

Excess weight can modify medication disposition in the body. Several pharmacokinetic studies suggest that excess body fat may alter the volume of distribution (Vd) and clearance (CL) of antibiotic medications, while drug absorption seems to remain unchanged.[6, 12, 38,39] Nevertheless, the degree to which these processes are affected depend on the hydrophilic and lipophilic properties of the drug. Both hydrophilic and lipophilic classes of antibiotics have been shown to have an increased volume of distribution and clearance rate in obesity. Table 2.2 shown below depicts the hydrophilic and lipophilic classes of antibacterial medications.

Table 2.2–Hydrophilic and Lipophilic Classes of Antibacterial Medications[36]

Table 2.2 Hydrophilic antibiotics have a tendency to dissolve in water, whereas lipophilic antibiotics disperse preferentially in adipose tissue or lipids.

HYDROPHILIC	LIPOPHILIC
β-Lactams	Fluoroquinolones
- Penicillins	Macrolides
- Cephalosporins	Lincosamides
Glycopeptides	Linezolid
- Vancomycin	Tetracyclines
Aminoglycosides	Sulfonamides

Generally, the distribution of hydrophilic drug correlates with lean body weight (LBW), whereas the distribution of lipophilic drugs correlates with total body weight (TBW). [36,39] Although hydrophilic antibiotic agents have a decreased ability to dissolve in adipose tissue, their volume of distribution may significantly increase in obese persons. This increase is mostly due to the fact that 30% of adipose tissue is composed of water as well as the fact that obese persons are more likely to have a higher lean body mass than normal weight persons standardized by height and sex.[98] Similarly, plasma volume increases with bodyweight.[99] A combination of these factors can eventually result in lower serum concentrations of hydrophilic antibiotic medications, potentially impairing the attainment of the MEC. On the other hand, distribution of antibiotic medications with high lipophilicity into fat generally increases as a result of adipose-tissue

binding, which decreases the amount of unbound drug available for pharmacological activity.[12] Therefore, lipophilic antibiotic drug classes may also necessitate a larger loading dose to achieve the desired effect in persons with excess weight. Additionally, obesity has been linked to increased hepatic and renal clearance of certain antibiotics, since liver and kidney volume and function positively correlate with lean body weight.[6,40] Increased clearance of antibacterial medications decreases half-life, which in turn affects the steady state concentration. It has been suggested that morbidly obese individuals may benefit from larger loading doses as well as shorter dosage intervals in order to achieve the desired therapeutic effect by compensating for modified drug distribution and clearance rates, respectively. However, dosing recommendations for the most commonly prescribed antimicrobial agents do not consider adjustment for body size or weight characteristics. The majority of pharmacokinetic evidence supports the notion that antibacterial medications should be given in higher initial doses to patients who have excess weight in order to better achieve therapeutic targets. [36]

2.2.3.2 Summary of Pharmacokinetic Evidence: Effect of Obesity on Pharmacokinetic (PK) Parameters by Antibiotic Class

Although antibiotic medications are generally issued in the oral form to outpatients in the primary care setting, most of the existing antibacterial pharmacokinetic (PK) literature has evaluated the impact of weight on intravenously administered antibiotics and associated outcomes (i.e. PK parameter changes and/or clinical outcomes). Obesity has been shown to alter the volume of distribution of antibacterial medications in most pharmacokinetic studies, whereas only some have reported a significant change in drug clearance.[12-13, 36, 100-108] Such modifications in PK parameters prompted researchers to recommend adjusting antibiotic dosage for weight. The following pharmacokinetic evidence summary is sorted by antibiotic class with the most available research data: aminoglycosides, vancomycin, β-lactams, fluoroquinolones, and linezolid.

Aminoglycosides and Vancomycin

Various PK studies have demonstrated that obesity may substantially increase the Vd and CL of vancomycin and aminoglycoside agents (e.g. gentamycin, tobramycin, amikacin). For vancomycin, 13 to 49% range increases in Vd have been observed, while the mean CL was found to be 2.3 to 2.5 times higher in obese subjects than in non-obese controls.[109-111] Similarly, a 9-58% range increase in Vd as well as a 15-91% range increase in the CL of aminoglycoside agents have been reported in obese patients when compared to non-obese and normal weight controls, respectively.[112-117] Accordingly, researchers recommend a weight-based loading dose for vancomycin and aminoglycoside antibiotics, since the modifications in Vd and CL generally impair the attainment of the desired drug concentrations (i.e. the MEC) using the standard dose.[13] However, due to risk of severe nephrotoxicity and ototoxicity that is dose dependent for both aminoglycosides and vancomycin, doses must be adjusted on the basis of routine measurement of peak and trough blood levels of such drug.[13]

β-Lactams

Despite the fact that the β-lactams comprise the largest antibiotic class, PK research is not as extensive for these agents in the context of obesity. Of the β-lactam subclasses, the cephalosporins dominate the available literature.[13] Cefotaxime and cefotiam, second generation cephalosporins, have been shown to have elevated Vd and CL in obesity, ranging from 42-68% and 14-63% increases, respectively.[118,119] Similarly, the Vd and CL of cefamandole also increased dramatically in obese patients when compared to historical normal-weight control patients.[120] This increase in Vd was postulated to be primarily the result of partial distribution and affinity of the drug to adipose tissue.[120,121] Cefazolin, a first generation cephalosporin, has been demonstrated to be more effective in achieving prophylactic clinical outcomes (e.g. preventing post-operative infection) when given to obese patients at double the standard dose; desired tissue and serum concentrations were reached with dose adjustment, which allowed for

comparable PK parameters to normal weight patients receiving the standard dose.[122]

The literature concerning penicillin pharmacokinetics in obesity is scarce. In the most recent case report, Newman and associates described a reduced serum concentration of the β-lactam antibiotic piperacillin/ tazobactam in a morbidly obese male patient with cellulitis who was given the standard dose of 3.375g every 4 hours.[102] Maximum drug serum levels in this morbidly obese patient remained below mean blood serum levels of a historical representative population of normal weight individuals receiving the same dose for greater than 50% of the time interval. Moreover, analysis revealed that Cmax was markedly reduced, while Vd and $t_{1/2}$ values were substantially increased as compared to the same representative population. As a result, it was shown that therapeutic targets were attained for only those bacteria with very low minimum inhibitory concentrations, which led the authors to suggest that using standard dosing regimens of piperacillin/ tazobactam may yield less than adequate exposures in morbidly obese patients and subsequently result in worse clinical outcomes.[102] In another case report, a dramatic increase in Vd was observed in an obese patient being treated with nafcillin, which prompted the authors to suggest that increasing the loading dose may be required for patients with excess weight.[123]

Finally, Chen and associates compared pharmacokinetic and therapeutic target attainment in 30 healthy adult volunteers stratified into 3 BMI groups (normal weight, class I/ II obesity and class III obesity with BMIs of 18.5 kg/m^2-24.5 kg/m^2, 30 kg/m^2-39.9kg/m^2 and ≥40 kg/m^2, respectively) using the recommended 1g once-daily dose of ertapenem, a carbapenem β-lactam antibiotic.[104] Results revealed that obese subjects had a significantly lower AUC and CL than their normal weight counterparts and the probability of attaining therapeutic targets were shown to modestly decrease with increasing BMI; this suggests that obese patients may require larger loading ertapenem doses than non-obese individuals.[4] In spite of the modest decrease in drug exposure observed in these obese subjects, who may need weight-based dosing adjustments, the clinical significance of this with respect to therapeutic outcomes is uncertain.[104] Thus, PK

evidence supports the notion of prescribing higher loading doses for cephalosporins as well as ertapenem; however, given the limited evidence for other β-lactam agents, proposing a weight-based dose adjustment for these subclasses is less obvious.

Fluoroquinolones

Among fluoroquinolone agents, ciprofloxacin has been the primary target of PK research with respect to obesity. The PK parameters of ciprofloxacin have been reported to change in the obese patient population; while one study claimed to have observed a significant increase in drug Vd and CL (21% and 23%, respectively),[124] another had reported a modest decrease in both Vd (5%) and CL (9%) parameters in 12 obese patients when compared to their normal weight counterparts.[100] Despite this discrepancy in findings, both research teams had suggested weight-based dosing guidelines for ciprofloxacin as this would improve tissue and plasma concentrations in obesity.[13] Hollenstein and colleagues demonstrated that adjusting the standard dose of ciprofloxacin according to total body weight allowed obese subjects (N=12) to achieve the same drug tissue distribution, CL and $t_{1/2}$ values as those found in lean subjects (N=12).[100]

Linezolid

Linezolid pharmacokinetics have also been researched in the obese patient demographic. In a case report, the Vd of linezolid was reported to have drastically increased in an obese male being treated for cellulitis with the standard recommended antibiotic dose. Furthermore, the patient's Cmax or peak concentration was markedly reduced as compared to previously recorded Cmax values for healthy subjects.[125] In contrast, Stein and colleagues measured serum drug concentrations over time in 7 obese outpatients being treated with a standard 600 mg dose of oral linezolid for cellulitis. Findings revealed that the drug tissue concentrations obtained in obese subjects were quite similar to those in historical healthy volunteers.[103] Despite reduced peak linezolid serum concentrations or Cmax in obese study subjects as compared with other clinical studies of normal

weight patients, all outpatients exhibited clinical cure at follow-up. However, further analysis revealed that prolonged antibacterial activity within the serum was observed against a variety of study bacterial isolates, with the exclusion of methicillin-resistant staphylococcus aureus (MRSA). Thus, the standard dose was considered effective for most bacteria isolates in this group of subjects.[103] Nevertheless, both reports observed a decreased Cmax in obese patients with similar linezolid dosing regimens, which indicates altered drug disposition in obesity and merits further pharmacokinetic research to determine whether dosing guidelines are appropriate for this patient population.[4]

2.2.4 Antibiotic Dosing Guidelines in Routine Clinical Practice

2.2.4.1 Evidence-Based vs. Current Dosing Recommendations for Antibacterial Medications in the Obese Patient Demographic

Weight-related dose adjustments for aminoglycoside and vancomycin medications have been strongly recommended as these classes of antibiotics are the most extensively researched in the field of pharmacokinetics.[13, 105-108] Because aminoglycoside antibiotics have been demonstrated to have large increases in Vd and CL in obese patients, adjusting loading doses for weight in order to compensate for these changes is advocated. An adjusted body weight (ABW = IBW + 0.4[TBW – IBW]) should be used to calculate initial loading dose, since dosing on total body weight (TBW) runs the risk of overdose, while the dosing interval should be appropriate for renal function. Similarly, the Vd and CL pharmacokinetic parameters of vancomycin are largely increased in obese patients and, thus, initial loading dose based on TBW is recommended, while intervals should be determined based on CL (15 mg/kg of TBW per 12 hrs or 10 mg/kg of TBW per 8 hrs). [13, 105-108] Because of convincing pharmacokinetic findings, the Infectious Disease Society of America (IDSA) have implemented these dosage adjustments for both vancomycin and aminoglycoside agents in the newest version of IDSA guidelines intended for the treatment of patients who have intra-abdominal infections.[107] The Sanford guidelines for antibiotic dosing have also included weight-based dosing for IV administered aminoglycoside and

vancomycin agents in their latest online Sanford Guide to Antimicrobial Therapy (2010).[126] In fact, weight-based dosing guidelines for adults do not exist for most antibacterial medications, despite the growing evidence linking excess weight to changes in drug disposition and therapeutic target attainment.

Certain β-lactam antibiotics have also been reported to have increased Vd and CL parameters in obese patients as compared to non-obese individuals. However, while Pai and colleagues suggest doubling initial standard doses in obese patients to compensate for these changes in their review paper,[13] Bearden and Rodvold recommend dosing based on adjusted body weight using a correction factor of 0.45 (i.e. ABW = IBW + 0.45[TBW-IBW]).[108] With respect to the fluoroquinolone class of antibacterial medications, conflicting evidence exists as to whether the pharmacokinetic parameters Vd and CL are significantly modified in obese as compared to non-obese patients.[13] Nevertheless, an individualized dosing regimen based on an adjusted body weight with a 0.45 correction factor for fluoroquinolones is generally recommended from research experts in this field. Overall, dosing most antibacterials on the appropriate body weight (TBW or ABW) for weight-based regimens and using a higher approved dose range for fixed-dose drugs are warranted in obese patients.[13, 107-108] Refer to Table 2.3 for the comparison of pharmacokinetic evidence-based dosing recommendations to current antibiotic dosing guidelines for obese adult patients.

2.2.4.2 Physician Adherence to Current Evidence-Based Antibacterial Dosing Guidelines in Obesity

Although recommendations concerning weight-related dose adjustments exist for particular antibiotic agents such as aminoglycosides,[127] the degree of physician adherence to and acceptance of such guidelines in routine clinical practice may be inadequate.[128,129] As a means of exploring the potential issues with implementation of evidence-based weight adjusted antibiotic dosing guidelines as well as the possible reasons for physician non-adherence, expert opinion papers were consulted. Falagas explains that "implementation of these ideas in routine clinical practice will entail substantial effort and cost, especially

because clinicians' longstanding attitudes towards prescription of antimicrobial agents will have to change."[36] Another barrier to guideline implementation mentioned by Falagas is time constraints in clinical practice, which may not allow for the appropriate antibiotic dosage calculations to be made. Most importantly, he says clinicians may be reluctant to give higher antibiotic doses to obese patients for the fear of toxic effects.[36] Accordingly, Erstad believes that clinicians may have the tendency to disregard weight-based dosing guidelines for the reason that the majority of pharmacokinetic studies "involved single IV doses given to small numbers of healthy volunteers or patients with relatively uncomplicated health status."[12] Therefore, the fact that recruited study patients are not representative of the 'typical' obese demographic may negatively affect physicians' decisions to follow a weight-based dosing approach for antibiotic medications based on data from existing studies. Furthermore, Erstad states that the lack of research demonstrating improved patient outcomes as a direct result of weight-adjusted dosing, either through increased medication efficacy or reduced toxicity, discredits the implementation of such guidelines.[12]

Table 2.3–Comparison of Evidence-Based Antibacterial Dosing Recommendations and the Sanford Guide to Antimicrobial Therapy for Obese Adult Patients

Table 2.3 Evidence-based dosing recommendations versus the current Sanford Guidelines to Antimicrobial Therapy in obese patients are presented for antibiotics with the most available pharmacokinetic data

ANTIBACTERIAL AGENTS	Vd	CL	EVIDENCE-BASED RECOMMENDATIONS FOR DOSAGE IN OBESE PATIENTS	SANFORD GUIDELINES		REFERENCES
				IV	ORAL	
1. Aminoglycosides	⇧	⇧	Dosing regimen based on adjusted body weight (ABW) with a correction factor of 0.4: ABW = IBW + 0.4 (TBW – IBW)	✓	**N/A**	Schwartz et al., 1978 Korsager, S. 1980 Sketris et al., 1981 Bauer et al., 1983 Leader et al., 1994 Traynor et al., 1995 Blouin et al., 1982 Ducharme et al., 1994 Bauer et al., 1998
2. Vancomycin	⇧	⇧	Dosing regimen based on total body weight (TBW)	✓	**N/A**	
3. β-Lactams						
a. Cephalosporins	⇧	⇧	Dosing regimen based on adjusted body weight using a correction factor of 0.45: ABW = IBW + 0.45 (TBW-IBW)	×	×	Yost et al., 1986 Mann HJ, Buchwald H. 1986 Yuk et al., 1988 Chiba et al., 1989 Forse et al., 1989 Lovering et al., 2001 Chen et al., 2006 Newman et al., 2007
b. Penicillins	⇧	—		×	×	
c. Carbapenems	—	⇩		×	**N/A**	
4. Fluoroquinolones						
Ciprofloxacin	⇳	⇳	Dosing regimen based on adjusted body weight using correction factor of 0.45: ABW = IBW + 0.45 (TBW-IBW)	×	×	Allard et al., 1993 Hollenstein et al., 2001 Pai MP, Bearden DT. 2007
5. Oxazolidinones						
Linezolid	⇧	—	Standard dose recommended Further PK research necessary	×	×	Mersfelder TL, Smith CL. 2005 Stein et al., 2005

2.3 ANTIBIOTIC TREATMENT FAILURE (ATF)

2.3.1 Definition, Prevalence, and Diagnosis of ATF

Although there is no consensus on the definition of antibiotic treatment failure, the word failure refers to "an event that does not accomplish its intended purpose."[130] Thus, in a general sense, antibiotic failure refers to the unsuccessful attempt of fully ridding the body of bacterial infection via the use of antibacterial medications, resulting in further treatment complications. Antibiotic treatment failure rates have been reported to range up to 64%, prompting researchers to investigate ATF causal mechanisms and predictors.[41] L.P. Garrod explains that the "causes of failure may be either in the nature of the diseases treated or in the choice or mode of use of the antibiotic."[131] Physicians make use of objective clinical criteria to detect the occurrence of ATF.[ii] Among the described criteria, treatment-based causes are the most frequent, particularly when antibiotic treatment is inadequate. Treatment failure is usually assessed within 72 hours upon hospital admission, while the standard test-of-cure follow-up physician visit is approximately one month later.[41] In primary care, antibiotic failure is considered as a diagnosis if there is a lack of improvement in the 48hours following initial antibiotic therapy or if infection symptoms have not resolved following the completion of the full course of antibiotic treatment.[132-134] Through numerous studies, significant patient-related ATF risk factors have emerged. While age, tobacco and alcohol consumption, as well as comorbidity status (e.g. chronic heart failure, diabetes mellitus, cardiac disease, interstitial lung disease) are all associated with a higher risk of ATF, receipt of influenza vaccine has been shown to act as a protective factor.[41]

2.3.2 Potential Causes of ATF

The most common antibiotic-related reasons for ATF occurrence in immunocompetent individuals include inappropriate use for infections that are not susceptible to antibiotic treatment (i.e viral infections), wrong choice of antibiotic (i.e. drug coverage that is too narrow), antibacterial resistance, drug-drug

[ii] Refer to Appendix 1, Table A1.2 for objective clinical criteria in the detection of ATF.

interactions, as well as unattained therapeutic targets from either irregular absorption or poor tissue distribution at the site of infection resulting from inadequate antibiotic dosage.[43] Patient-related variables potentially responsible for ATF include non-compliance to the physician recommended antibacterial dosing regimen, comorbidities, smoking and alcohol consumption, which can affect antibiotic metabolism.[135] From this list of potential ATF causes, only therapeutic target attainment and antibacterial resistance have been shown to be problematic in patients with excess weight when compared to normal weight individuals, while there is no evidence to suggest that the remaining causes differ between weight groups.[iii]

2.3.2.1 Antibacterial Resistance

Antibacterial resistance is a major concern when discussing the possible causes of ATF. It is no surprise that resistance rates among several microorganisms are on the rise in developed countries, particularly methicillin-resistant S.aureus (MRSA), vancomycin-resistant enterococci (VRE), extended spectrum beta-lactam (ESBL)-resistant enteric Gram-negative bacilli (*Klebsiella* and *Enterobacter* species) and penicillin-resistant *Streptococcus pneumoniae* (PRSP). PRSP is often found in the community, while the others are commonly associated with nosocomial-acquired infections and, therefore, rarely encountered at the primary care level.[136] Nonetheless, the Public Health Agency of Canada (PHAC) reported that 21% of all identified MRSA cases during the 2007 calendar year were community-acquired, where the majority of MRSA rate increases had been previously found to be primarily located in the provinces of Quebec and Ontario.[44] Moreover, PRSP rates were found to be 22.5% and 24.4% for Ontario and Quebec during the 1997 to 1998 period, respectively.[137]

In the primary care setting, MRSA has emerged as one of the most frequent causative microorganisms in community-onset skin and soft tissue infections (SSTIs), particularly in cellulitis.[138] Moreover, Schneider-Lindner and

[iii]Refer to Appendix 1 for further details on other possible causes of ATF and their associated predictors.

colleagues conducted a cohort study of over 20 000 primary care patients using the General Practice Research Database, where they found that obesity was a significant and independent predictor of MRSA (OR 1.27; 95% CI 1.10–1.45).[139] In light of this, empirical treatment choices for community-acquired SSTIs have been evaluated and researchers have recommended that primary physicians prescribe trimethoprim-sulfamethoxazole and clindamycin to patients with suspected MRSA infections.[140] On the other hand, risk of PRSP infection have been shown to be influenced by patient age, previous use of antibiotics, alcoholism, and the presence of a non-invasive disease; however, patient weight characteristics were not shown to correlate with the acquisition of PRSP-caused infections.[141]

Although certain bacterial serotypes may demonstrate antibiotic susceptibility in vitro, resistance may also occur during the course of therapy (typically from the use of subinhibitory antibiotic doses) or post-therapy.[43] A recent systematic review evaluating the effect of antibiotic prescribing in primary care on resistance in individual patients found that temporary post-therapy resistance was most likely to occur within 2 to 12 months of initial antibiotic treatment for respiratory tract bacteria (pooled OR of 2.4; 95% CI 1.3-4.5). For urinary tract infections, post-therapy resistance was higher at 2 months following initial antibiotic treatment (pooled OR of 2.5; 95% CI 2.1-2.9), but may persist up to 12 months (pooled OR 1.33; 95% CI 1.2-1.5).[142]

2.3.2.2 Unattained Therapeutic Targets via Inadequate Antibiotic Dosage

If antibiotic medications fail to reach the site of infection at the minimal effective concentrations required in order to exert their desired pharmacological effects, treatment failure generally ensues. Irregular absorption of the drug from the intestinal tract and/or poor tissue distribution are the primary reasons for unattained therapeutic targets at the site of infection. Adequate drug tissue distribution is heavily dependent on the vascular system as well as the hydrophilic or lipophilic properties of the antibacterial with regard to its transportation and intracellular uptake, respectively. Accordingly, unattained therapeutic targets or

insufficient antibiotic concentrations at most infected anatomical sites are typically the result of: i) vascular insufficiency or (ii) altered pharmacokinetic parameters (i.e. increased Vd and/or CL rate). Inadequate local antibiotic activity is commonly due to insufficient dosage. [43]

As described previously (refer to section 2.2.4.1), individuals with excess weight have been shown to have a modified antibacterial drug-tissue distribution profile as compared to their normal weight counterparts, while intestinal absorption remains unchanged. The observed increases in Vd and, in some cases, CL for antibiotic medications in obese patients may impair the ability of the drug to reach the MEC required for clinical success. In light of this pharmacokinetic evidence, the drug tissue distribution changes accompanying excess weight may make attaining therapeutic targets exceedingly difficult with increasing degrees of obesity, particularly since antibiotic guidelines recommend standard dosing regardless of patient body size or weight characteristics. Therefore, the modifications of key pharmacokinetic parameters in obese individuals may ultimately lead to antibiotic treatment failure.

Given that patient BMI is not a predictor for inappropriate antibiotic use, the selection of narrow-spectrum antibiotic agents or patient non-compliance, the probability of such variables causing ATF in obese individuals is relatively equal to that of their normal weight counterparts. Therefore, antibacterial resistance and insufficient antibiotic dosage remain the prime candidates for causing ATF in patients with excess weight.

2.4 EXCESS WEIGHT AND ANTIBIOTIC TREATMENT FAILURE

2.4.1 Review of Published Studies Regarding the Association Between Excess Weight and Antibiotic Treatment Failure

Although the topic of adjusting antibiotic dosing guidelines for body size and weight characteristics has been gaining popularity among researchers, only one relevant study has evaluated whether weight is associated with treatment failure. In Italy, Abdullahi and associates were the first to conduct a small prospective cohort study (excess weight study group N=40, normal weight control

group N=41) to investigate the link between treatment failure and BMI; their objective was to evaluate the influence of BMI on the efficacy of eradication treatment in 81 naïve non-diabetic outpatients with H. pylori infection.[143] The standard H. pylori eradication therapy regimen given to both the control and study groups consisted of two weeks of 40 mg pantoprazole as well as 1g amoxicillin and 250 mg of clarithromycin three times a day for the first week of treatment. Results revealed that efficacy of eradication therapy was associated with BMI, where the normal weight control group was 4.77 times more likely to exhibit clinical cure in comparison to the excess weight group (overweight and obese patients). The authors hypothesized that the eradication failure rate was higher in patients with excess weight due to the "physiological changes associated with obesity, which may influence the volume of distribution of medications, potentially leading to sub-therapeutic concentrations.[143]" They suggested that "alternative treatment regimens with higher dose and/or longer duration may be necessary in patients with excess weight to achieve a higher eradication rate.[143]" However, no further analysis was performed as a means of investigating the postulated link between the lack of weight-based dosing therapy and the risk of eradication failure. On the other hand, other studies have examined the effect of excess weight and antibiotic dosing regimens on infection prophylaxis in the context of surgery, where most have reported higher post-operative infection rates (or antibiotic failure rates) among obese patients receiving standard doses of antibiotics as compared to normal weight patients.[144-146] Finally, a retrospective database study evaluated risk factors for clinical failure in hospitalized patients with intra-abdominal or skin/soft tissue infections and concluded that obesity had no effect on the health outcome.[147]

2.4.2 Conclusion of Literature Review

To date, no population-based study has addressed whether excess weight is directly associated with antibiotic treatment failure, although there have been some indications in the literature that this may be the case. Evidence suggests that obese persons have a substantially higher risk of infection and hospitalization as

compared to normal weight patients.[29, 31] Moreover, a significant increase in antibiotic prescribing rates in the obese population has been described at the primary care level.[33] With the discovery that excess weight does indeed have an impact on medication pharmacokinetics, certain antibiotic dosing regimens are being questioned and reviewed. Because antibiotic medications have minimum effective concentrations, which are extremely important in the attainment of therapeutic targets, the modifications in volume of drug distribution and systemic clearance rate in obese individuals may necessitate dosing adjustments to compensate for changes in the loading or maintenance of antibiotic doses, respectively. However, most antibiotic medications are approved as standard dosing regimens disregarding the pharmacokinetic differences associated with body size and composition characteristics, particularly pertinent for obese patients.[36] While the problem of underdosing is less of a concern for medications taken over a longer time frame as dosages are generally adjusted over time, it presents a major challenge for medications specifically given for acute conditions such as antibiotics.[38,108] Therefore, I postulate that the underdosing of antibiotic medications, resulting from the lack of weight-related dose adjustment, can potentially impair the attainment of the MEC in individuals with excess weight, a direct cause of treatment failure.[iv]

Despite sufficient pharmacokinetic evidence to support the consideration of weight-based dosing for the most commonly prescribed antibiotic medications in routine clinical practice, the uptake of such evidence-based recommendations continues to remain at a standstill.[36] Clinicians argue that the lack of research demonstrating improved or poorer patient outcomes as a direct result of weight-adjusted or standard dosing, respectively, discredits the support of and/or implementation of such guidelines.[12] The present study intends to address this current gap in the literature by investigating the link between excess weight and a poor clinical outcome, antibiotic treatment failure, and whether this may be due to a lack of weight-based dosing.

[iv] Refer to Appendix 1, Figure A1.2 for theoretical model.

3.0 METHODS

3.1 STUDY DESIGN

A historical cohort study was conducted from an existing Régie de l'assurance maladie du Québec (RAMQ) dataset generated from the IRB-approved population-based follow-up study "Estimating age, gender and risk factor specific incidence rates of stroke and cardiovascular disease using longitudinal cohorts created from linkage of survey and administrative databases." (CIHR funded project) (N Mayo PI) The original cohort consisted of all Quebec residents who were uniquely sampled in the 1992 and 1998 Santé Québec health surveys and was determined through two phases. The first phase entailed probabilistic sampling to identify households eligible for participation within geographically defined areas of the 16 regions of the province; this yielded a total household response rate of 85% for 1998 and 88.5% for 1992 (see Bellerose et al. for further details on household eligibility).[148] In the second phase, one person from each of the participating households aged 15 years and older with the ability to speak English or French was randomly selected to complete the personal health questionnaire. A total response rate of 86% and 84% was achieved in the second sampling phase for the 1992 and 1998 health surveys, respectively.[148-149] However, data from these health surveys were made available for only those who consented to having their health insurance number linked to provincial administrative databases. Of the total 46 474 persons sampled from both Santé Québec health surveys, 18 014 (38%) consented to having their health insurance number used for linkage with the survey data. Data contained within the provincial health administrative databases for consenting respondents were available from the year preceding the date of the survey as well as all years subsequent to and including 2007. There were no statistically significant differences between consenting and non-consenting patients with respect to age, sex, education and financial resources. Participants were followed-up to

2007, with the final sample comprising 17 826 persons. Of this final sample, 485 participants were missing weight and/or height information (2.7%).

In order to achieve thesis objectives, a subcohort comprising of all consenting health survey participants, who had received at least one oral antibiotic prescription or hospital admission for an acute infection from the date of the health survey until December 2005, was assembled by merging data retrieved from provincial population (RAMQ) health databases using an encrypted patient identifier. Detailed information was collected from the Santé Québec population-based health surveys and RAMQ databases (see section 3.2 for the description of databases), the latter of which contained data regarding all health care utilization claims, including those for hospitalizations, physician visits, and prescription medications. From this subcohort, exclusion criteria were applied to define the final study population, which was subsequently used for the assessment of weight status and the occurrence of antibiotic treatment failure. Details concerning exclusion criteria can be found in Section 3.3 (Defining the Study Population).

3.2 DATA SOURCES

3.2.1 RAMQ Beneficiary Demographic Database

The RAMQ beneficiary demographic database provides data on age, gender, postal-code linked data on income and education based on the 2006 Statistics Canada enumeration area mapping[150], language preference, prescription drug insurance status and mortality of all study participants in the dataset.[151]

3.2.2 RAMQ Medical Service Claims Database

Because of the universal health care system, all medical services are covered by the provincial health insurance system for Quebec residents. Physicians are compensated on a fee-for-service basis for all medical services provided in a hospital or clinic setting after submitting a claim for each medical encounter to the RAMQ, which documents key patient- and service-related variables.[152] Accordingly, the medical service claims database offers information

regarding the beneficiary provincial health insurance number, the procedure code assigned to the medical service provided, the type and location of service delivery (e.g. emergency, inpatient, ambulatory services), and the International Classification of Diseases 9th revision of diagnostic codes (ICD-9) for all medical services billed by physicians, which accounts for approximately 86% of all services.[153] In April of 2006, RAMQ implemented the new ICD-10 diagnostic coding system, while the ICD-9 coding system was used up to March 2006.[154] Because ICD-9 mapping to ICD-10 diagnostic codes is difficult and may cause inconsistency, the ICD-10 index was not used and follow-up for this study was restricted to December of 2005. Since this process is the only manner in which physicians can be reimbursed for their services, it is assumed that this administrative database is both complete and accurate.[152]

Validity of ICD-9 diagnostic coding contained within the medical service claims database was performed by comparing "gold standard" diagnoses abstracted from the medical charts of 14 980 patients, Quebec senior residents enrolled in the MOXXI study, to those retrieved from this administrative database. Despite the variation in sensitivity among particular conditions, the medical service claims data was found to have a high degree of specificity when it came to the accuracy of its diagnostic codes with respect to the medical charts. Furthermore, Wilchesky and associates recommend the use of this administrative database along with all data pertaining to physician billings for research purposes as a means of correctly obtaining the diagnostic profiles of the patients under study.[155] Similarly, other studies have validated specific treatment procedure codes (e.g. polypectomy) alone,[156] and in combination with diagnostic codes for particular conditions of interest (injury ascertainment) obtained from the medical service claims database and the authors have concluded that its specificity and sensitivity values were appropriate for use in research.[157]

3.2.3 RAMQ Prescription Claims Database

The prescription claims database provides information on each drug dispensed including codes for the prescription drug, dosage, strength, generic

name and American Hospital Formulary (AHF) class, as well as the quantity, cost, date and duration of each prescription. It also contains the patient identification number (PID), professional class, prescribing physician and encrypted dispensing pharmacy identification codes.[158] However, prescription claims data were only available for study participants covered by the Quebec Public Drug Insurance Plan, which is typically intended for persons aged 65 years and older, recipients of last-resort financial assistance (i.e. welfare recipients), persons not eligible for a private plan through their employer as well as children of persons covered by the public health plan.[159] The public drug insurance plan is estimated to cover approximately 50% of Quebec residents, while others are required to be under a private plan as this is mandatory by legislation.[151] Thus, study participants who were covered by a private drug insurance plan were excluded from this database.

Tamblyn and colleagues have demonstrated that the prescription claims database is one of the most accurate means of describing drug information by comparing database entries to clinical data; as a result, this database can be extremely useful for assessing drug exposure and physician prescribing variables.[160] In assessing the completeness of the prescription claims database, Tamblyn and colleagues examined 1 917 214 records of dispensed prescriptions in the year of 1990 for a stratified random sample of 65 349 senior patients living in Quebec. Only 0-0.4% of database records had missing information in key drug fields (e.g. identifiers, drug, quantity, date dispensed and duration). Of clinical records, 723 filled prescriptions by 306 elderly patients in one internal medicine clinic were selected for the evaluation of database accuracy. The prescription claims database showed that 599 prescriptions (83%) were dispensed to the patient as well as correctly identified the patient and the type of drug, whereas the identification of the prescribing physician was found to be documented accurately in 89% of the 599 prescriptions successfully linked to the database via patient health insurance number and drug identification number (DIN). In addition, the quantity and duration of the prescriptions were valid in 69.1% and 72.1% of records, respectively. However, dosing information accuracy was shown to have

some limitations, particularly for prescriptions filled for an extended period of time (60 to 90 days).[160]

3.2.4 MED-ECHO Database

The MED-ECHO or hospitalization database from the Ministère de la Santé et des Services Sociaux (i.e. Quebec Ministry of Health and Social Services) contains admission and discharge information for all acute care hospitalizations in Quebec, which is based on medical chart review and hospital records. It includes PID, type of health care institution, date of admission and discharge, length of stay, death and death 48 hours prior to or after admission, type of physician, primary and secondary diagnoses (up to a maximum of 15) using ICD-9 codes, discharge destination as well as treatment codes.[158]

A number of studies have evaluated the validity and reliability of the MED-ECHO hospital discharge database; it is considered as the gold standard for estimating both the inhospital length of stay and the number of hospitalizations.[161-165] Studies validating the MED-ECHO database were done by comparing hospital discharge codes to medical charts, which established this database as a valid and complete source of hospitalization records. Accordingly, its reliability was evaluated by Delfino and associates who showed that the percent agreement of discharge diagnoses ranged from 76-95% for respiratory conditions as well as 93% agreement for non-respiratory diagnoses.[161]

3.2.5 Santé Québec Health Surveys

The 1992 and 1998 self-reported health surveys contain data on the following variables at baseline for the participants included in this study: (i) demographic information, (ii) tobacco use, (iii) alcohol consumption, (iv) use of drugs and/or other psychoactive substances, (v) nutrition habits, (vi) physical activity, (vii) body mass index (BMI) calculated from self-reported height and weight, (viii) perceptions of health status, (ix) health problems, (x) accidents or injuries, (xi) mental health status, (xii) thoughts of suicide, (xiii) disability or mobility impairments, (xiv) health care service use, (xv) medication consumption,

(xvi) family, (xvii) support network, (xviii) work and health status, (xix) social conditions, and (xx) spirituality/religion and health status.[149] All questions on both self-administered health surveys were validated and proved as reliable prior to the distribution of surveys to the general population, since the majority of questions were re-used from the 1987 Santé Québec population-based health survey.[148] Demographic information, body mass index (BMI), health problems as well as tobacco and alcohol consumption data were readily available for analysis for patients consenting to have their health insurance number linked to administrative databases.

Table 3.1–Description of RAMQ Administrative Databases and Health Survey

Table 3.1 Data contained within each of the RAMQ administrative databases as well as the 1992 and 1998 Santé Quebec Health Surveys are presented.

MED-ECHO	PRESCRIPTION CLAIMS	MEDICAL SERVICE CLAIMS	BENEFICIARY DEMOGRAPHIC	HEALTH SURVEY
Data on Acute Care Hospital Admissions for all Quebec Residents: • Discharge diagnoses • Date of admission • Duration of hospital stay • Treatment received inhospital	Data on Each Drug Dispensed: • Drug name • Drug dosage • Date and duration of each prescription • Prescribing physician • Dispensing pharmacy	Data on All Medical Services Compensated on a Fee-For-Service Basis: • Health insurance number of beneficiary • Date and type of medical service • ICD-9 diagnostic codes • Type and location of service delivery	Data on Beneficiary: • Age • Gender • Postal-code linked data on income and education • Enumeration area mapping patient language preference, prescription drug insurance status and mortality	Data on baseline risk factors and exposure: • Demographic information • Body Mass Index (BMI) • Health problems - comorbidity • Tobacco use • Alcohol consumption

3.3 STUDY POPULATION: IDENTIFICATION OF STUDY COHORT

For the purpose of this historical cohort study, the sampling frame consisted of all adult individuals who had received at least one oral antibiotic prescription or hospital admission for acute infection throughout the course of

follow-up, which ranged from the date of the health survey up to and including December 2005 for this study. Selected study subjects were within the normal weight (BMI of 18.5 kg/m^2 to 24.9 kg/m^2), overweight (BMI of 25 kg/m^2 to 29.9 kg/m^2) and obese (BMI of ≥30kg/m^2) weight classes aged 20-79 years. It was expected that the overweight and obese weight classes would have the largest number of adverse health outcomes (ATFs), since obese persons are more susceptible to infection and excess weight significantly modifies antibiotic medication pharmacokinetics. Patients missing weight and/or height measurements, identified as pregnant or who have had any form of bariatric surgery from the date of the health survey to the time of receipt of their first antibiotic prescription or hospitalization for acute infection (defined as T_0) were not included as this would influence the body mass index and/or inappropriately classify these individuals as overweight or obese. Patients with chronic infectious diseases such as tuberculosis (TB) or a recent history (30 days preceding the assigned T_0) of a non-acute infection that may require 4 weeks or more of antibiotic therapy were excluded.[v] The impaired immune function of these individuals as well as the complex treatments for these types of infections would have led to a higher incidence of infection recurrence and perhaps higher ATF rates due to other potential causes, which may have biased the results. Subjects who were not covered by the Quebec public drug insurance plan spanning from T_0 to the end of outcome assessment (i.e. T_1= T_0+ 30 days) were not included in the study cohort. Other participants who had died of a non-infectious cause or who were lost to follow-up during the outcome assessment period were also excluded. In addition, study participants who were found to have a history of recent antibiotic use (i.e. any antibiotic or hospitalization for infection) in the 30 days prior to first receipt of an oral antibiotic or hospital admission for acute infection were removed from the study cohort as these would qualify as additional antibiotic therapy rather than 'first' or 'new' users initially sought for study

[v]Please see Appendix 2, Table A2.2 for a list of non-acute infections (in red) requiring 4 or more weeks of antibiotic therapy.

objectives.[vi] Although a wide variety of potential confounding variables exist such as sociodemographic variables, lifestyle risk factors (tobacco and alcohol consumption), inappropriate antibiotic use and resistance, as well as the presence of comorbidities (e.g. malignancy, cardiovascular, metabolic, autoimmune deficiencies, liver and renal disorders), these subjects were nonetheless included in this cohort study, while confounders were adjusted for in the statistical model.[vii]

Subjects meeting the above eligibility criteria were selected from an existing provincial health insurance (RAMQ) dataset; relevant information was retrieved for only those consenting Quebec health survey respondents with unique health insurance numbers from the RAMQ databases. To assess whether the sample was representative of the general population, a comparison of study demographic variables for the drug cohort (i.e. patients covered by the public drug insurance plan) to the general population was performed via the use of data from the Santé Québec population-based health surveys.[viii] Usage of an existing database was ideal in relation to the objectives of this cohort study for feasibility reasons, since employing a prospective design would be exceedingly expensive and time-consuming. By taking advantage of the accessibility of patient data provided by participants who consented for linkage to health administrative databases from the 1992 and 1998 Quebec health surveys, there was no need for further data collection on the target population given that the original cohort sample size was quite large, consisting of 18 014 persons living in Quebec.

[vi] Because RAMQ data was available for the year prior to the date of the health survey, we were able to determine whether recent antibiotic use was an issue for participants having their T_0 near the date of the 1992 health survey.

[vii] For details concerning the creation of variables during the selection process while defining the study population, please refer to Appendix 2 (A2.1).

[viii] Appendix 2 demonstrates the representativeness of the study sample (see Table A2.1)

3.4 MEASURES

3.4.1 Exposure: Excess Weight

3.4.1.1 Body Mass Index (BMI)

The gold standard for measuring excess weight has long been the percentage body fat method; however, such direct methods are impractical because of the need for technical tests (whole body immersion) as well as being expensive and time consuming. Thus, body mass index (BMI) has been popularly adopted for epidemiological studies simply for feasibility reasons. BMI is calculated by taking the quotient of the individual's measured body weight in kilograms and square of the height in meters. According to the WHO, an adult is considered overweight, when their BMI is within the 25 kg/m^2 to 29.9 kg/m^2 range and obese if their BMI is $\geq$ 30 kg/m^2, while normal weight corresponds to a BMI within the 18.5 kg/m^2 to 24.9 kg/m^2 range.[10-11] However, because BMI is not a direct measure of body fat, a small proportion of people may have been placed in a higher BMI category even though they did not have excess body fat (e.g. athletes). Nevertheless, evidence suggests that there is a dose-response relationship between BMI and the risk of developing chronic diseases such as coronary heart disease, hypertension, type II diabetes and premature death.[166] The WHO reports that excess fat is strongly correlated with an increased relative risk of developing chronic disease.[167] Furthermore, BMI has also been used as an indicator in other populations to predict relative risk of morbidity and mortality.[168] The BMI was computed for each participant as a continuous value; the category (normal weight, overweight and obese) in which each participant belongs was also reported.

The BMI calculations for each subject were based on weight and height measurements reported by the participants from the self-administered Santé Québec Health Surveys at baseline. Although self-reported measures have been shown to have inherent biases, where participants frequently under report weight and over report height,[169-171] most large epidemiological studies depend on this method for the calculation of BMI as it facilitates the collection of data from large population samples while decreasing the burden and expense of clinical

measurements of height and weight.[172, 173] Nonetheless, several studies have demonstrated that self-reported values are a valid and reliable means of estimating height and weight measurements.[171, 174-181] Reliability studies regarding BMI values obtained from self-report surveys have concluded that this method is quite reliable with kappa values ranging from 0.8-0.87.[181] McAdams and associates have demonstrated that although self-reported BMI is often lower than technician measurements, the correlations between self-report and measured BMI values were quite high ($\geq$0.90), while both technician and self-reported measures were equally correlated with disease markers such as fasting glucose (r = 0.43), high density lipoprotein cholesterol (r = -0.53) and systolic blood pressure (r = 0.54). In addition, the comparison of disease biomarker correlates between percentage body fat and BMI were similar. [173]

The bias associated with self-reported weight and height measurements underestimates the true prevalence of overweight and obese persons in a given population-based sample, which may cause misclassification bias in the results (i.e. a person who has a true BMI in the overweight category may have been misplaced in the normal weight category due to reporting bias).[173] In order to control for such bias, a correction regression model developed by Statistics Canada was used to estimate the actual BMI corrected for age, sex, and self-reported BMI factors (refer to formula below for BMI correction formula).[182] In addition, the RAMQ databases were searched for ICD-9 codes corresponding to obesity (278.0, 278.8) in combination with CCP codes for gastric partitioning or bariatric surgery status (56.2, 56.93, 56.59) as a means of accounting for weight shifts during the course of follow-up. This method of confirming bariatric surgery occurrence has been used elsewhere.[183] Similarly, pregnancy was also identified via ICD-9 codes (650, 660-669, V27.0-V27.7) or CCP codes (84.0-86.2, 86.8-86.9, 87.98) corresponding to delivery from the date of the survey to 6 months post-T_0.[184]

Statistics Canada: BMI Correction for Self-Reported BMI Values[182]

Male: -1.08 + (1.08 x self-reported BMI)
Female: -0.12 + (1.05 x self-reported BMI)

3.4.1.2 BMI and Antibiotic Dosing Practices: Lack of Weight-Based Dosing

Despite pharmacokinetic evidence supporting the implementation of weight-based dosing for commonly dispensed antibiotics in primary care, [13] current dosing guidelines do not consider weight. Therefore, to evaluate the second study objective of determining whether current dosing practices are associated with the health outcome (ATF), antibiotic daily dose (DD) as well as DD to BMI ratios were computed for each subject using the formula below and were reported as continuous variables per weight group.

$$\left(\frac{\text{total number of pills}}{\text{duration of prescription in days}}\right) \times \text{dosage per pill in mg} = \text{DD (daily dose) in mg}$$

Data on antibiotic dosage, number of pills, and duration of prescription in days were retrieved from the prescription claims database. In the event that the dosage code in the prescription claims database reported a range of antibiotic dosages (e.g. 125 mg-500mg), the highest dosage was selected in the calculation of the DD in order to remain conservative, since the study hypothesis concerns the lack of weight-based dosing or underdosing of obese individuals as a potential cause of ATF.

3.4.2 Outcome: Antibiotic Treatment Failure (ATF)

As mentioned previously, there is no consensus with regard to a standardized definition of antibiotic treatment failure; however, ATF is considered to have occurred when it is detected via the use of objective clinical criteria.[41] Among patient-based, treatment-based and test-based criteria for ATF diagnosis, treatment-based methods were the most feasible in the assessment of antibiotic treatment failure health outcomes from the RAMQ dataset.[ix] Thus, ATF was measured via secondary antibiotic prescriptions or hospitalizations with infection as a primary or secondary cause of admission within a one month time frame following initial treatment for infection. Previous historical cohort studies have shown strong associations between the specific predictors of interest and

[ix] A summary of the clinical criteria used to diagnose ATF can be found in the Appendix 1 (see Table A1.1).

antibiotic treatment failure, with ATF defined as any additional antibiotic therapy subsequent to initial treatment.[46, 185-187] Other studies have demonstrated strong correlations between hospitalizations for infections and ATF as a cause of admission.[46, 188] The number of cohort subjects with secondary antibiotic prescriptions and/or hospitalizations for an infectious cause were retrieved from the RAMQ databases during the specified time frame dictated by the outcome assessment period (see figure 3.1 below).

A new or 'first' antibiotic prescription was defined as the first receipt of a drug identified to be an orally administered antibacterial by the RAMQ *liste de medicaments* and associated AHF codes with no other oral antibiotic medication issued from the date of the health survey completion. A 'first' hospitalization for infection was defined as any acute care hospital admission with a length of stay (LOS) of 30 days or less for an infectious cause requiring a short course of antibiotic therapy (21 days or less) and identified as such via ICD-9 codes of interest.[x] The time at which the first antibiotic was dispensed to cohort subjects or the discharge date of the first hospitalization for an infectious cause, whichever came first, was referred to as T_0. Because it is common practice to prescribe an oral antibiotic regimen as a continuation of IV antibiotic therapy received in hospital, the hospital discharge date was used as T_0, rather than the date of admission.

Secondary antibiotic prescriptions were defined as the addition of one or more antibiotic medications of any form (including parenteral) or as a complete or partial switch from the initial regimen to another antibiotic regimen within the month following T_0. A 30-day time interval for assessing whether a secondary or additional antibiotic had been dispensed to each cohort subject was selected as this corresponds to the time required in clinical practice to evaluate if symptoms have resolved for a range of acute infections, referred to as 'the test of cure' physician visit.[41] Therefore, T_1 was used to denote the cutoff time for outcome assessment, while the outcome assessment period was defined as T_0+3 days to T_1. The 3 day grace period instated after T_0 has been used in other ATF studies, since

[x] Refer to Appendix 2, Table A2.2 for ICD-9 codes of interest.

treatment failure is typically assessed 3 days after the initial infection diagnosis and allows sufficient time for initial antibiotic therapy to target the suspected causal microorganism.[189] Data on all antibiotic prescriptions dispensed in primary care were obtained from the RAMQ prescription claims database. Please refer to Table 3.2 for the RAMQ list of oral antibacterial medications (e.g. capsule, tablet or oral suspension formulation) under study at T_0 and their corresponding AHF codes.

Table 3.2–Main Oral Antibiotics by AHFS Class Code in the RAMQ Liste Des Medicaments

Table 3.2 Oral antibiotic medications and classes under study are presented. *AHFS = American Hospital Formulary Service

Class (AHFS* Class Code)	Oral Antibiotic Medications
Cephalosporins (081206)	Cephalexin, Cefaclor, Cefuroxime, Cefadroxil
Macrolides (081212)	Erythromycin, Spiramycin, Clarithromycin, Azithromycin, Telithromycin
Penicillins (081216)	Phenoxymethylpenicillin, Amoxicillin, Cloxacillin
Quinolones (081218, 082200)	Ciprofloxacin, Ofloxacine, Norfloxacin, Levofloxacin, Moxifloxacin
Sulfonamides (081220)	Trimethoprim/Sulfamethoxazole
Tetracylines (081224)	Doxycycline, Tetracycline, Minocycline
Miscellaneous Antibacterials (081228)	Vancomycin, Clindamycin
Urinary Anti-infectious Agents (083600)	Trimethoprim/Sulfamethoxazole, Nitrofurantoin
Miscellaneous Anti-Infectious Agents (084000)	Clindamycin, Metronidazole, Erythromycin Ethylsuccinate/Sulfisoxazole Acetyl
Skin Agents: Other Antibacterials (840404, 840416)	Metronidazole

Hospitalizations were defined as any admission to an acute care hospital facility for an infectious cause. For secondary/additional hospitalizations occurring during the outcome assessment period, patients were considered to have an episode of ATF if the primary or secondary cause of admission was that of an

acute or non-acute infection as well as potential complications of infections (e.g. bacteremia, septicemia, osteomyelitis etc). Verification of possible causes for hospitalization was performed via the identification of ICD-9 diagnostic codes relating to an acute or non-acute infectious conditions (including complications), which were retrieved from the RAMQ databases.[xi] Hospitalization data was obtained and verified from the assessment of both the provincial hospital discharge (MED-ECHO) and medical service claims databases of the RAMQ, respectively. Aside from the Med-Echo hospital discharge database, the medical service claims has also been shown to be a valid and accurate alternate measure to estimate hospital admissions; Monfared and LeLorier illustrated that there was a total agreement between Med-Echo and the RAMQ medical service claim database on the date and duration of hospitalizations with a 7-day grace period.[152] Therefore, the current method of hospitalization data retrieval for the creation of this RAMQ dataset is quite accurate.

The outcome assessment period for this second working definition of ATF was adjusted based on the two T_0 groups that patients belonged to within the infection cohort. For patients having their T_0 correspond to a hospitalization for infection, a hospital readmission or even death as a result of an infectious cause was considered an ATF event if it occurred between T_0 and T_1. This adjustment was made since the selection of such patients was based on a diagnosis of infection at admission, where in-hospital antibiotic therapy ensued and, therefore, any hospital readmission for infection after the date of discharge (T_0) was considered as treatment failure. However, the outcome assessment period remained T_0 + 3 days to T_1 for the group of patients having their T_0 associated with first receipt of an oral antibiotic prescription, where an additional hospital admission for infection would only qualify as an ATF event if it occurred 3 days post-T_0 up to and including T_1. Figure 3.1 depicts a summary of the assessment periods used in order to ascertain the occurrence of an ATF event stratified by the different infection groups at T_0.

[xi] ICD-9 codes corresponding to additional infectious causes of secondary admissions are also listed in Appendix 2.

Figure 3.1– Defining the Outcome Assessment Period and ATF Events

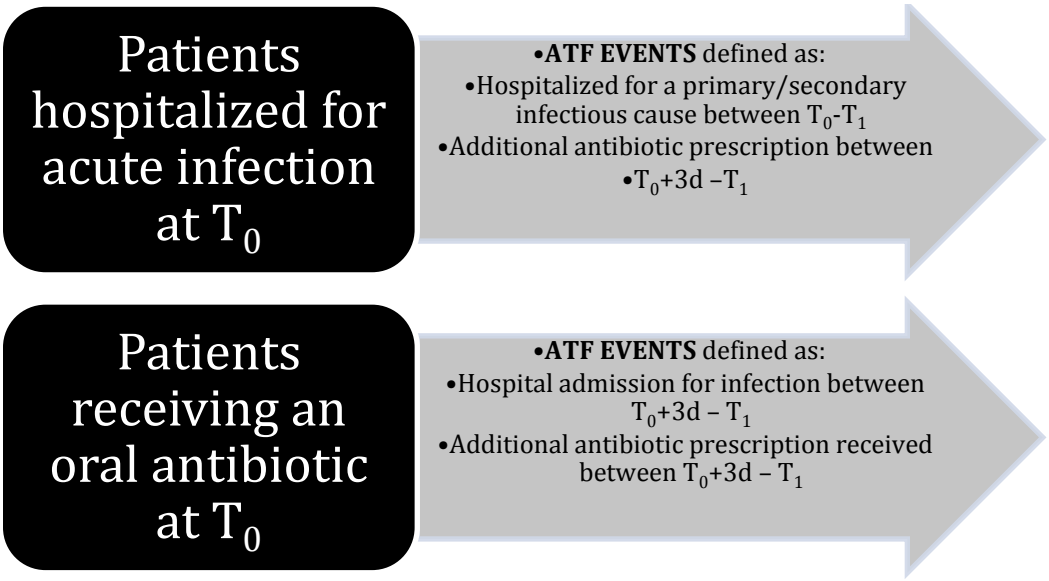


Figure 3.1 Patients were split into two groups depending on the type of initial antibiotic therapy at T0. The outcome assessment period for each group is presented on the right.

3.4.3 Potential Confounders and Covariates

3.4.3.1 Sociodemographic Variables

Sociodemographic variables may potentially modify the relationship between excess weight and antibiotic failure. Age, gender and postal code approximations of income and education were retrieved from the RAMQ beneficiary demographic database as well as self-reported data from the Quebec Health Surveys at baseline. Studies have demonstrated that age is significantly associated with risk of ATF for patients with community acquired pneumonia and complicated intra-abdominal infections.[46, 190] ATF has been previously reported to occur more frequently among males when compared to their female counterparts. [190-191] Socioeconomic status (SES) has also been linked to obesity prevalence, both in men and in women.[192] SES was defined based on household income, where study participants were placed within low, middle and high income categories.[xii]

[xii]Please refer to Appendix 2, Table A2.5 for the working definitions of low, middle and high income, which was in agreement with those used in the Santé Québec Health Surveys.

3.4.3.2 Life-Style Risk Factors

Life-style factors such as tobacco and alcohol consumption are likely to confound the association between excess weight and ATF. Previous evidence suggests an increased incidence of smoking and heavy drinking in patients with ATF.[190-191, 193] Smoking was categorized into never and current-ever smoker groups at the time of the health survey. The definition for heavy drinking was in agreement with that of the Santé Québec Health Surveys, whereby heavy drinkers were identified as such if they consumed 29 or more alcoholic beverages during the 7 days preceding the completion of the health survey.[17, 149] All life-style habits were retrieved from the self-report Santé Québec Health Surveys at baseline. Patients having missing information from the Santé Quebec health surveys at baseline for the life-style risk factors of interest were dealt with by placing them into the risk category (i.e. missing smokers were placed in the smoker category, missing drinkers were placed in the drinking category etc.).

A meta-analysis of studies examining the validity of self-reported smoking habits as compared to biochemical assessments reported overall acceptable sensitivity (mean = 87.5%) and specificity (mean = 89.2%) estimates of self-reported smoking habits.[194] Although reliability of the Santé Québec health survey was not reported for these life-style variables, other studies have evaluated the reliability of a self-reported survey on alcohol consumption. Williams and colleagues reported that the average Pearson correlation coefficient (r) estimates of reliability computed by the alternate forms, test retest and combined methods were 0.91 concerning self-reported alcohol use from a general population survey.[195] Data retrieved on life-style risk factors will be dichotomous in nature (i.e. yes/no) and will be used to adjust for confounding in the analysis.

3.4.3.3 Comorbidity

The presence of comorbidities can potentially confound results; cardiovascular, respiratory and metabolic as well as other relevant diseases proven to either increase or decrease the likelihood of having ATF were documented.[46, 188, 190-191, 193] Additionally, the prevalence of obesity-related

comorbidities such as hypertension, diabetes and cardiovascular disease are on the rise.[196] Therefore, it is essential to adjust for these variables in order to achieve an unbiased association between exposure (excess weight) and outcome (ATF). Three data sources were used to identify patient comorbidities for the chronic conditions of interest as well as to account for potential discrepancies between the self-report Quebec Health Surveys and the physician billing data that were retrieved from the RAMQ database. First, the MED-ECHO database was searched for hospital discharge ICD-9 codes identifying any of the co-morbid conditions of interest. Second, the medical service claims of the RAMQ database was also searched for the visit records (office, clinic or emergency) with comorbidity-specific ICD-9 codes. Finally, the self-reported comorbidities in the section "health problems" of the Quebec Health Surveys were retrieved as a measure of comprehensiveness.

The Charlson index was used to measure comorbidity as it is the most extensively studied and commonly used in clinical research, particularly for predicting mortality.[197] The Charlson Comorbidity Index (CCI) is based on the diagnoses of 17 disease conditions, which were selected for their strong associations with mortality.[197-199] Charlson index scores (1, 2, 3, or 6) are assigned based on mortality risk for the associated condition. Despite being a established hospital-based measure of mortality risk,[199] the CCI is now frequently being used for comorbidity measurement in ambulatory populations.[200] In a critical review of available methods for measuring comorbidity, Groot and colleagues named the Charlson index as one the most reliable and valid measures for comorbidity in clinical research.[198] CCI has been shown to have high levels of concurrent (>0.40 correlation coefficients),[201-206] predictive and construct validity; predictive validity being of most importance, since CCI was significantly associated with mortality, hospital readmissions and length of stay.[199, 203, 206-217] According to this critical review, test-retest reliability was acceptable, while interrater reliability was shown to be moderate to good.[202, 204, 212, 218] Although the gold standard for determining accurate Charlson index scores is from medical chart review, scores were weighted based on data retrieved from the medical service claims of the

RAMQ database. By verifying score accuracy with the medical service claims data as compared to medical chart data, Wilchesky and associates found that there was little or no disparity between the CCI score computed from the administrative data as compared to that from the medical chart.[155] With respect to this study, the CCI variable was created by abstracting ICD-9 diagnostic codes for conditions of interest from the MED-ECHO and medical service claims databases as well as the health survey data. [xiii]

3.4.3.4 Inappropriate Antibiotic Use and Antibacterial Resistance (MRSA)

Prescribing antibiotics inappropriately for viral infections occurs in primary care, although such practices seem to be on the decline in the past decade. Nevertheless, inappropriate use of antibiotics can lead to ATF, which may confound the association between exposure and outcome. In order to account for this, the time of year, particularly the first (January to March) and fourth quarters (October to December) known as influenza season, will serve as a proxy measure for antibiotic inappropriateness and will be adjusted for in the statistical model; Glass and associates assessed the 2006 CIPARS data in relation to macrolide prescribing patterns and found that use was highest from October to March, which was significantly associated with the rate of influenza.[219]

Antibacterial resistance is another concern when assessing the occurrence of ATF. Although MRSA acquisition is much less common in the community setting, it is quite prevalent among skin and soft tissue infections, specifically among obese patients with cellulitis.[44] In order to account for this in the community setting as well as in the hospital setting, the type of infection (i.e. SSTIs commonly linked with MRSA) was used in the statistical model as a potential confounder. For patients either admitted to an acute care hospital facility or receiving oral antibiotics at T_0 or at the time of ATF, the ICD-9 codes corresponding to a skin or soft tissue infections typically associated with

[xiii] Refer to Appendix 2 for the list of co-morbid conditions covered under the CCI, their corresponding ICD-9 codes and associated score (see Table A2.3).

MRSA[220] were retrieved from the MED-ECHO database as well as the Medical Service Claims database.[xiv]

3.4.3.5 Previous History of Antibiotic Use

Because the provincial health administrative databases hold prescription data concerning the antibiotic medications dispensed within the year preceding the health survey and the BMI data retrieved from the health survey itself was pivotal for analyzing the association between exposure and outcome, patients whose first antibiotic prescription or hospitalization for infection (at T_0) occurred during the same year as the completion of the health survey were investigated for previous history of antibiotic use (i.e. hospitalization for infection or previous antibiotic use). Similarly, patients who have received any form of antibiotic (including parenteral) in the year preceding T_0 also fell under this category. Ideally, cohort subjects should have a minimum one year time interval between previous antibiotic use and those labeled as "new or first" at T_0; this one-year interval was chosen as a means of controlling for temporary antibacterial resistance induced through previous antibiotic use, which has been shown to last anywhere from 2 to 12 months post-treatment.[142] Thus, patients with a history of previous antibiotic use in the year preceding their assigned T_0 as determined by the investigation of medical prescription records were accounted for in the statistical model.

3.5 SAMPLE SIZE

Sample size calculations were based on the primary objectives of estimating a difference in proportions for antibiotic treatment failure per weight category. This calculation was based on inferences for proportions assuming two independent samples with the normal approximation to the binomial distribution. The selected two independent samples were the overweight and normal weight categories, since the difference between these proportions would have been the

[xiv] Refer to Appendix 2, Table A2.4 for a list of ICD-9 codes and conditions used to define MRSA-SSTIs, which was included as a proxy for antibacterial resistance.

most difficult to detect in comparison to obese and normal weight samples. Using the BMI category sample statistics from the original RAMQ dataset, the ratio of overweight to normal weight individuals was 0.71. Assuming that the proportion of ATF occurring in the normal population has a range of 10-60% with an 80% power level and a type I error rate (α) of 0.05 for a two sided hypothesis, the sample size needed to detect a 5% difference in proportions would range from 864-1 933 for the normal weight group and 614–1 373 for the overweight group. This range of sample size estimations is provided in the table below. Given the prevalence of bacterial infection in the community, the selected population for this study has met the cut-off sample size estimates required to detect 5% differences between proportions. This estimation was quite conservative given our total sample of 17 341 persons with available weight and height measurements; of the total sample, 8 153 fall in the excess weight categories (12.6% are obese). Because the sample size calculation is based on comparisons between the overweight and normal weight persons, the effect size for comparisons between obese and normal weight patients will likely be higher, providing ample power to detect larger differences expected to be seen between these weight categories. G.E. Dallal's PC-Size POWPAL program was used to calculate the range of sample size cut-offs to achieve 80% power (see Table 3.3).

Table 3.3–Range of Sample Size Cut-Offs Between Normal and Overweight Groups to Achieve 80% Power

Table 3.3 The sample size estimates shown above were calculated using G.E Dallal's PC-Size POWPAL Program

Proportion of Outcome in Normal Weight Patients (P_1)	Proportion of Outcome in Overweight Patients (P_2)	Sample Size (N)	
		Normal Weight	Overweight
10%	15%	864	614
20%	25%	1358	965
30%	35%	1701	1208
40%	45%	1893	1345
50%	55%	1933	1373
60%	65%	1822	1294

3.6 STATISTICAL ANALYSES

3.6.1 General Descriptive Statistics

Basic descriptive statistics were produced to describe the study sample and test relationships between key variables using correlations, which were used to characterize important features of the group as well as aid in the verification of data accuracy and consistency (data cleaning). Additionally, the most common antibacterial medications prescribed as well as the most common infection indications at T_0 stratified by weight group were reported.

3.6.2 Main Hypothesis: Excess weight is a significant predictor of ATF

This study tested the hypothesis that overweight and obese persons receiving an antibiotic prescription will have a higher proportion of antibiotic treatment failures (ATFs) in comparison to normal weight persons as indicated by secondary antibiotic prescriptions or hospitalizations for infections in the month following initial therapy, independent of age, gender, SES, comorbidity, smoking and drinking as well as other antibiotic-associated confounders. Because ATF was reported as a dichotomous categorical variable and the exposure variable was also classified into three categories (normal, overweight and obese weight classes), a binary logistic regression model was employed, which assumes that observations are independent of one another. As ATF events were restricted to only the first for every study patient and a repeated measures design was not used, this assumption of independence held true. A stepwise-selection approach was used and variables included in the logistic regression model were CCI score, life-style factors (smoking and drinking categories), time of year of initial antibiotic prescription (i.e. flu season), type of infection (i.e. MRSA-SSTIs), history of antibiotic use along with forced variables BMI category (i.e. overweight and obese), age category, gender and SES class (i.e. low, middle and high income).[221] Cut-off significance values were 0.10 for entry into the model and 0.15 for exit.

3.6.3 Secondary Hypothesis: Current dosing practices are associated with ATF

This study also tested the secondary hypothesis, which states that a lack of weight-based antibiotic dosing is associated with ATF occurrence. Firstly, this hypothesis assumes that the ratio of the initial dose of antibiotic medications divided by the patient's body BMI will be lower in overweight and obese patients as compared to normal weight persons (reflecting a lack of weight-based dosing). In order to evaluate this second study objective, a subgroup analysis involving only those patients receiving an oral antibiotic prescription at T_0 was performed. Initial antibiotic daily dose at T_0 was plotted as a function of BMI, the latter reported as a continuous variable to verify whether there was a dose-response relationship with BMI. Initial antibiotic daily dose (DD):BMI ratios were calculated per subject within each group and group ratio means were compared between obese and normal weight as well as overweight and normal weight categories using student t tests. Similarly, the mean antibiotic daily dose was computed for each weight category and compared between groups using Tukey-Kramer adjustment tests for multiple comparisons.[222] The null hypothesis, which states that the DD:BMI ratio means or mean antibiotic daily dose between weight groups is equal, was rejected based on a p value < 0.05. As part of a secondary analysis, additional predictors that may affect ATF occurrence (dependent variable) were evaluated using stepwise multiple logistic regression analysis.[221] Variables included in the secondary ATF model were CCI score, life-style factors (smoker and drinker categories), time of year of initial antibiotic prescription (i.e. flu season), type of infection (i.e. MRSA-SSTIs) and history of antibiotic use covariates along with forced sociodemographic factors (e.g. age, gender) as well as additional dosing predictor variables such as DD:BMI and type of prescriber (family physician vs. other prescribers).

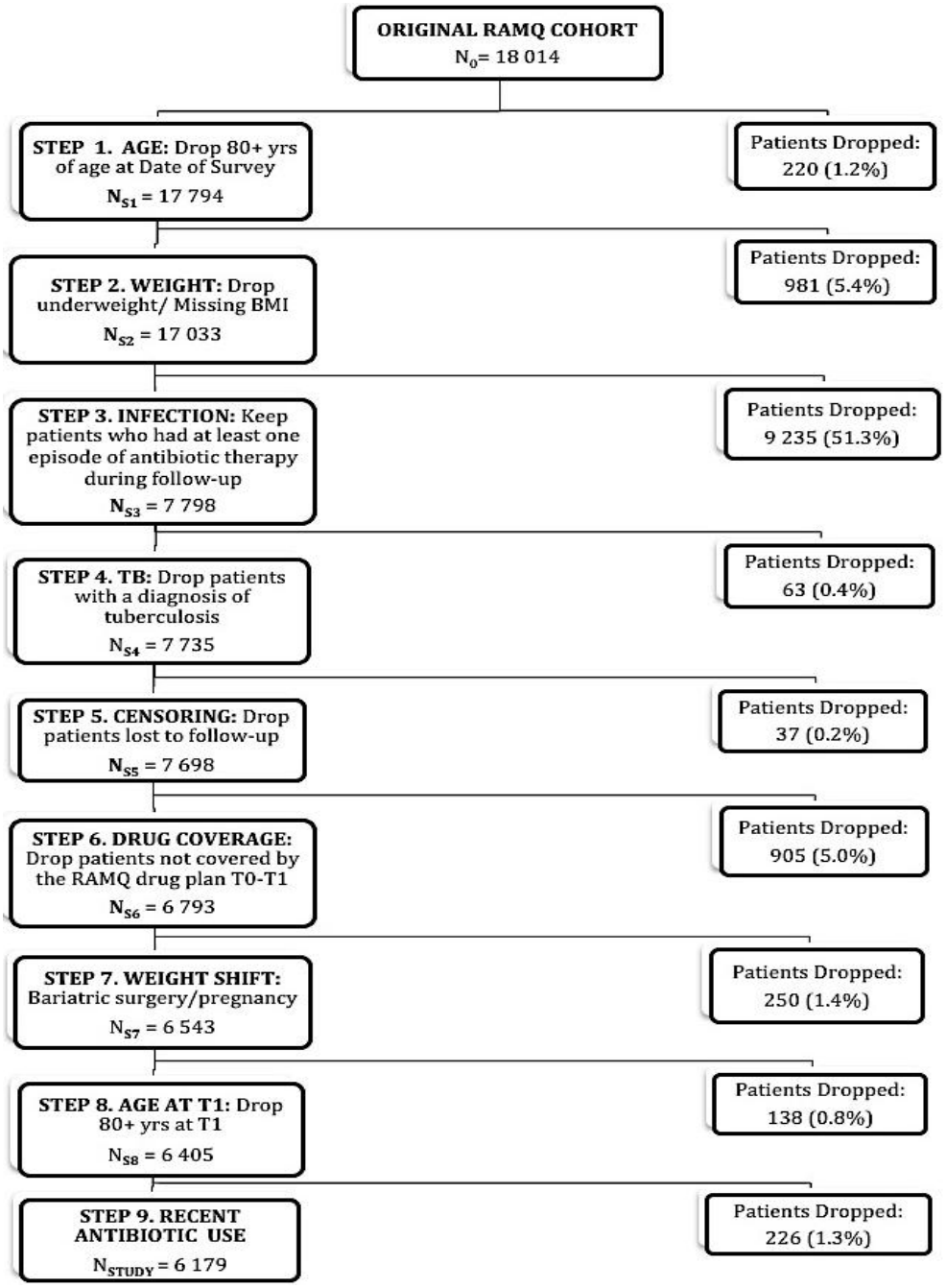
Although the Vd and CL of hydrophilic and lipophilic classes of antibiotics may differ, additional subgroup analyses involving the categorization of antibiotics (e.g. hydrophilic/lipophilic) in order to evaluate their effects on ATF were not performed, as the power cut-offs for such calculations would not be met.

4.0 RESULTS

4.1 DESCRIPTIVE RESULTS

After applying all relevant exclusion criteria to the original RAMQ cohort, the final study sample size was 6 179, where 39.0% and 21.4% of which fell under the overweight and obese weight categories, respectively. Figure 4.1 depicts the study population selection process and the number of participants retained after each exclusion criterion step was applied.

Figure 4.1-The Study Population Selection Process



Of the 6 179 patients, 828 (13.4%) were confirmed to have had an ATF event during the outcome assessment period; while 807 ATF episodes were due to additional prescriptions or modifications in antibiotic regimens, 21 were the result of a hospital admissions/re-admissions or death with an infectious cause. Baseline characteristics of the study population stratified by ATF are presented in Table 4.1 shown below.

For patients receiving an oral prescription at T_0, the most commonly prescribed antibiotic AHF classes and antibacterial medications were described by weight group in addition to the overall totals. The overall top 5 AHF antibiotic classes in descending order were: 1) penicillins (34.9%), 2) macrolides (18.4%), 3) quinolones (14.3%), 4) cephalosporins (12.5%), and 5) miscellaneous antibiotics (11.2%). Penicillins and macrolides were the most prescribed AHF antibiotic classes in each weight class with a dispense percentage of approximately 35% and 18% per group, respectively. While quinolones were the third highest prescribed among antibiotic classes for both normal weight (14.1%) and overweight groups (15.1%), cephalosporins placed third in the obese weight class with a dispense rate of 13.9%. The remaining antibiotic class prescribing frequencies were similar between weight groups. With respect to the most frequently prescribed oral antibacterial drugs at T_0, the overall top 5 in descending order were: 1) amoxicillin (16.0%), 2) ciprofloxacin (9.2%), 3) phenoxymethylpenicillin (8.8%), 4) trimethroprim/sulfamethoxazole (8.6%), and 5) clarithromycin (8.5%). Although amoxicillin was the most commonly dispensed in all three weight groups, there was some variability in subsequent frequency rankings of oral antibacterial medications prescribed among normal, overweight and obese weight classes. For instance, phenoxymethylpenicillin was the second most dispensed oral antibacterial medication in the normal weight group (9.3%), whereas it descended to fifth among the obese weight class (8.2%). Clarithromycin, cloxacillin and cefuroxime were the only oral antibiotics prescribed to patients with excess weight more frequently than their normal weight counterparts (clarithromycin 8.9% vs. 7.7%; cloxacillin 5.9% vs. 5.4%; cefuroxime 4.4% vs. 3.8%). Moreover, metronidazole, doxycycline, and

cephalexin were unique antibiotic medications to the normal, overweight and obese groups, respectively. Figures 4.2 and 4.3 illustrate the most commonly prescribed oral antibacterial AHF classes and medications by weight group.

Table 4.1 – Baseline Characteristics of the Study Population

Table 4.1 Baseline characteristics of the study population stratified by ATF are presented. The "other comorbidities" category includes HIV infection, dementia, hemiplegia/paraplegia, and rheumatologic CCI conditions. Frequencies in these categories were grouped rather than reported separately for danger of numbers being under the RAMQ-required reporting restriction of 5 persons per cell*

Characteristics	N (%)		
	Patients w/o ATF (N= 5 351)	**Patients w/ ATF (N_{ATF}= 828)**	**Total (N_{TOT}= 6 179)**
Gender			
Female	3010 (56.3)	443 (53.5)	3 453 (55.9)
Age (yrs)			
20-34	766 (14.3)	115 (13.9)	881 (14.3)
35-49	1 189 (22.2)	184 (22.2)	1 373 (22.2)
50-64	1 432 (26.8)	216 (26.1)	1 648 (26.7)
65-79	1 964 (36.7)	313 (37.8)	2 277 (36.9)
SES			
Low Income	1 760 (32.9)	287 (34.7)	2 047 (33.1)
Middle Income	3 209 (60.0)	497 (60.0)	3 706 (60.0)
High Income	382 (7.1)	44 (5.3)	426 (6.9)
Weight Group			
Normal	2 143 (40.1)	301 (36.4)	2 444 (39.5)
Overweight	2 088 (39.0)	320 (38.6)	2 408 (39.0)
Obese	1 120 (20.9)	207 (25.0)	1 327 (21.5)
Smoking			
Never	1 361 (25.4)	214 (25.8)	1 575 (25.5)
Current-Ever	3 990 (74.6)	614 (74.2)	4 604 (74.5)
Drinking			
Non-Drinkers	1 483 (27.7)	263 (31.6)	1 746 (28.3)
Non-Heavy Drinkers	3 498 (65.4)	511 (61.7)	4 009 (64.9)
Heavy Drinkers	370 (6.9)	54 (6.5)	424 (6.9)
CCI Score			
0	3 691 (69.0)	558 (67.4)	4 249 (68.8)
1	968 (18.1)	153 (18.5)	1 121 (18.1)
2+	692 (12.9)	117 (14.1)	809 (13.1)
Comorbid Conditions			
Myocardial Infarction	190 (3.6)	38 (4.6)	228 (3.7)
Congestive Heart Failure	124 (2.3)	25 (3.0)	149 (2.4)
Peripheral Vascular Disease	76 (1.4)	13 (1.6)	89 (1.4)
Cerebrovascular Disease	161 (3.0)	23 (2.8)	184 (2.9)
Chronic Pulmonary Disease	747 (14.0)	129 (15.6)	876 (14.2)
Peptic Ulcer Disease	155 (2.9)	14 (1.7)	169 (2.7)
Diabetes	363 (6.8)	71 (8.6)	434 (7.0)
Diabetes w/ Complications	57 (1.1)	9 (1.1)	66 (1.1)
Liver/Renal Disease	85 (1.6)	16 (1.9)	101 (1.6)
Primary Cancer	225 (4.2)	31 (3.7)	256 (4.1)
Metastatic Cancer	90 (1.7)	15 (1.8)	105 (1.7)
Other Comorbidities*	82 (1.5)	13 (1.6)	95 (1.5)

Figure 4.2– Most Commonly Prescribed Oral Antibacterial AHF Classes by Weight Group

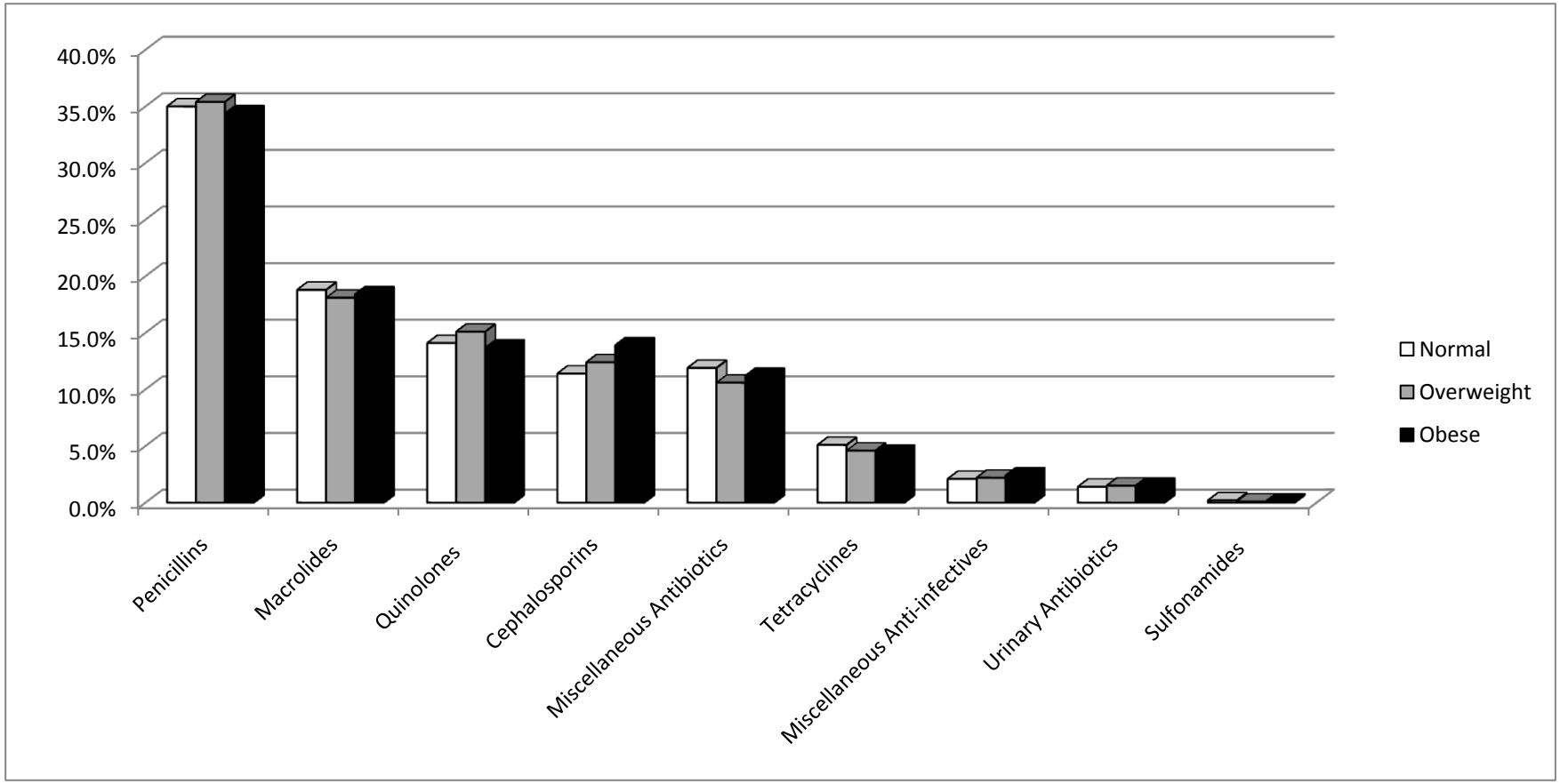


Figure 4.2 - Most commonly prescribed antibacterial classes for study patients receiving an oral prescription at T_0 stratified by weight class. Percentages presented in the chart were calculated based on weight group rather than total dispense rates.

Figure 4.3– Most Frequently Prescribed Oral Antibacterial Medications by Weight Group

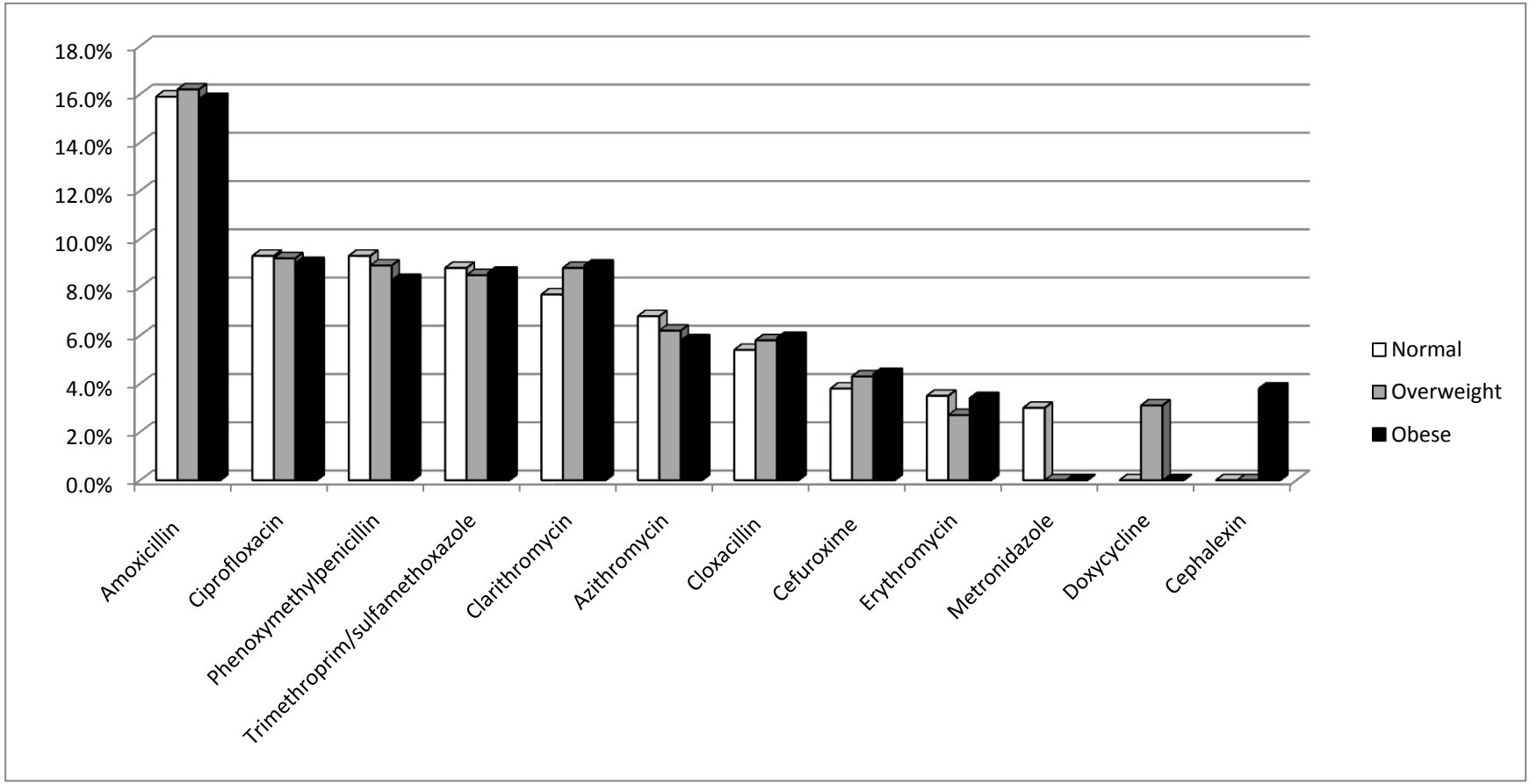


Figure 4.3 Most frequently prescribed antibacterial medications for study patients receiving an oral prescription at T_0 stratified by weight class. Percentages presented in the chart were computed based on weight group rather than total dispense rates.

In addition to antibacterial medication descriptive statistics, the most common infection indications for antibiotic therapy at T_0 were also produced. Interestingly, only 1 625 (26.3%) of patients receiving a form of antibiotic therapy had documented ICD-9 codes corresponding to infection, while the remaining 4 554 (73.7%) confirmed to have been dispensed an oral antibiotic medication (via the prescription claims database) after a medical consult had no evidence of infection diagnostic coding in the Medical Service Claims database. Furthermore, the weight category that had the least documented ICD-9 codes for infection was that of the obese (74.8%). Table 4.2 illustrates the lack of coding for infections within RAMQ databases by weight group.

Table 4.2 – Coding of Infections in the Medical Service Claims Database

Table 4.2 The frequencies of ICD-9 codes corresponding to a diagnosis of infection for patients proven to have received antibiotic therapy are reported. All those missing coding for a diagnosis of infection at T_0 (i.e. infection type is 0) were in the Medical Service Claims database.

TOTAL NUMBER OF INFECTION TYPES AT T_0	NORMAL N (%)	OVERWEIGHT N (%)	OBESE N (%)	TOTAL N (%)
0	1 795 (73.0)	1 766 (73.3)	993 (74.8)	4 554 (73.7)
At least 1	649 (27.0)	642 (26.7)	334 (25.2)	1 625 (26.3)
Total	2 444	2 408	1 327	6 179

Of the patients who had available infection diagnoses in either the MED-ECHO or Medical Service Claims databases, 42 patients had multiple infections (2 or more infection diagnoses) at T_0. Among all weight categories, upper respiratory tract infections (URTIs), lower respiratory tract infections (LRTIs) and skin and soft-tissue infections (SSTIs) were the most frequently reported antibiotic indications with overall dispense rates of 30.3%, 24.0%, and 14.2%, respectively. LRTIs were more commonly diagnosed indications among overweight (26.9%) and obese individuals (24.6%) as compared to their normal weight counterparts (20.9%). Similarly, SSTIs were more prevalent among the excess weight classes (overweight 15.3%; obese 14.7%) than the normal weight group (12.9%). Urinary tract infections (UTIs) occurred more often in normal weight and overweight categories, while gastrointestinal tract infections (GITIs) and ear and/or eye infections as well as abscesses were more common in the

obese weight category. Table 4.3 summarizes the most common infection indications for initial antibacterial therapy by weight group at T_0.

Table 4.3– Most Common Infection Indications for Antibacterial Therapy at T_0

Table 4.3 Most common infection indications by weight category are presented for all patients at T_0. Upper respiratory tract infections URTIs, lower-respiratory tract infections LRTIs, skin and soft tissue infections SSTIs, urinary tract infections UTIs and gastrointestinal tract infections GITIs. The "other" category includes infections of unspecified causes and/or infections that are typically considered to be of rare occurrence.

INFECTION TYPE	NORMAL WEIGHT N (%)	OVERWEIGHT N (%)	OBESE N (%)	TOTAL N (%)
URTIs	224 (33.5)	183 (28.0)	98 (28.3)	505 (30.3)
LRTIs	140 (20.9)	176 (26.9)	85 (24.6)	401 (24.0)
SSTIs	86 (12.9)	100 (15.3)	51 (14.7)	237 (14.2)
UTIs	66 (9.9)	63 (9.6)	27 (7.8)	156 (9.3)
GITIs	64 (9.6)	55 (8.4)	37 (10.7)	156 (9.3)
Genitoveneral	31 (4.6)	20 (3.1)	13 (3.8)	64 (3.8)
Abscess	23 (3.4)	27 (4.1)	16 (4.6)	66 (3.9)
Other	25 (3.7)	19 (2.9)	11 (3.2)	55 (3.3)
Ear/Eye	10 (1.5)	11 (1.7)	8 (2.3)	29 (1.7)
Total	669	654	346	1 669

4.2 PREDICTORS OF ATF

Initially, a crude logistic regression model (*Model 1*) was created with obesity and overweight as the sole predictors of the ATF outcome (e.g. ATF = intercept + overweight + obesity). The crude slope (β_{CR}) estimate for overweight and obesity was 0.09 (95% CI 0.0-0.2) and 0.3 (95% CI 0.2-0.4) with corresponding odds ratios (ORs) of 1.09 (95% CI 0.92-1.29) and 1.32 (95% CI 1.09-1.59), respectively; however, only obesity was found to be significant in the model with a p-value of 0.005. Firstly, exploratory preparatory logistic steps were performed where each covariate was added alone with forced variables obesity and overweight in the ATF model to determine significance. Of all potential confounding variables and covariates, only MRSA, history of antibiotic use and drinker category were found to be significant, while sociodemographic factors as well as smoker status, CCI score, and the proxy for inappropriate antibiotic prescribing 'flu season' were non-significant. Next, a saturated model (*Model 2*) with all covariates and confounding variables was produced and obesity continued

to be a significant predictor of ATF with an adjusted OR of 1.25 (95% CI 1.03-1.52), while overweight remained non-significant. Other statistically significant predictors of ATF in the saturated model included non-drinkers (adjusted OR of 1.19, 95% CI 1.01-1.41), MRSA (adjusted OR of 2.33, 95% CI 1.78-3.06), and history of antibiotic use (adjusted OR of 1.27, 95% CI 1.08-1.50) as suggested previously during preparatory logistic regression steps. Table 4.4 summarizes parameter estimates, standard errors (SE) and ORs (95% CI) for the ATF saturated model.

Table 4.4–Excess Weight and ATF: Parameter Estimates and ORs of the Saturated Model

Table 4.4 The saturated model for predicting ATF includes all confounding variables and covariates listed in the table. For multi-level variables such as SES, age and drinker, the reference group was taken to be the most commonly reported level among categories. Therefore, the 65-79 yrs, middle income, and non-heavy drinker categories were taken as reference groups. All reported parameter estimates (β_{ADJ}) or OR values (OR_{ADJ}) are adjusted for the remaining variables included in the model. Variables were considered to be significant if p-values<0.05.

VARIABLE	PARAMETER ESTIMATES		ODDS RATIOS	
	β_{ADJ}	SE	OR_{ADJ}	95% CI
1. Gender (male=0)	-0.1	0.08	0.88	0.75-1.03
2. Age Category				
20-34 yrs	0.0005	0.1	1.00	0.78-1.28
35-49 yrs	0.03	0.1	1.03	0.84-1.27
50-64 yrs	-0.001	0.1	1.00	0.83-1.21
3. SES Category				
Low Income	0.007	0.08	1.01	0.86-1.19
High Income	-0.3	0.2	0.77	056-1.07
4. Overweight	0.06	0.09	1.06	0.89-1.26
5. Obesity	0.3	0.1	1.25	1.03-1.52
6. Drinker Category				
Non-drinker	0.2	0.09	1.19	1.01-1.41
Heavy Drinker	-0.02	0.2	0.98	0.72-1.33
7. Smoker	-0.04	0.09	0.97	0.81-1.15
8. CCI Score				
1	-0.01	0.1	0.99	0.81-1.21
2+	0.03	0.1	1.03	0.82-1.29
9. Flu Season	0.01	0.08	1.01	0.87-1.18
10. MRSA	0.8	0.1	2.33	1.78-3.06
11. History of Antibiotic Use	0.2	0.08	1.27	1.08-1.50

In determining the final best-fitting logistic regression model for predicting antibiotic treatment failure using stepwise selection, the Akaike's Information Criterion (AIC), deviance, and Hosmer-Lemeshow (H-L) goodness of fit statistics were consulted and compared with the saturated and crude model values. During stepwise selection, the 'smoker' and 'CCI score' confounding variables as well as the covariate 'flu season' were removed as they were not significant predictors of ATF, whereas only the 'MRSA', 'history of antibiotic use' and 'drinker category' covariates met the 0.1 significance level for entry into the logistic regression model; these were retained in addition to exposure variables (i.e. overweight and obesity) and sociodemographic factors (i.e. age, gender and income), which were forced into the final stepwise model. This model (*Model 3*) had the least explanatory variables with lower AIC (4 834.4) and deviance values (4 808.4) as compared to the crude (AIC 4 866.3; deviance 4 860.3) and/or saturated models (AIC 4 842.2; deviance 4 808.2), while demonstrating good fit of observed values represented by the non-significant H-L p-value of 0.1.

After selecting the final ATF model based on the best goodness of fit statistics with the least explanatory variables (i.e. *Model 3*), the adjusted effect of obesity on ATF risk was found to remain statistically significant with an OR of 1.26 (95% CI 1.03-1.52), nearly equivalent to values in the saturated model. Similarly, the non-drinker category, MRSA and history of antibiotic use also remained statistically significant in the final ATF model. Table 4.5 presents the crude and adjusted ORs with their corresponding 95% confidence intervals in the final selected ATF model.

Table 4.5– Excess Weight and ATF: Crude and Adjusted Effects of the Final Model

Table 4.5 The final model produced using stepwise selection with forced selection of gender, age and socioeconomic status (SES) categories as well as overweight and obesity variables. The crude and adjusted ORs along with their associated 95% confidence intervals are presented for the variables included in the final ATF model. Reported point estimates under the crude effects grouping (i.e. OR_{CR}) do not consider other explanatory variables when predicting ATF, whereas OR_{ADJ} is adjusted for the remaining predictors listed in the table. Variables were considered to be significant if p-values<0.05.

VARIABLE	CRUDE EFFECTS	ADJUSTED EFFECTS
	OR_{CR} (95% CI)	**OR_{ADJ}* (95% CI)**
1. Gender (male=0)	0.90 (0.77-1.04)	0.88 (0.76-1.03)
2. Age Category		
20-34 yrs	0.94 (0.75-1.19)	1.00 (0.78-1.27)
35-49 yrs	0.97 (0.80-1.18)	1.03 (0.84-1.26)
50-64 yrs	0.95 (0.79-1.14)	0.99 (0.82-1.20)
3. SES Category		
Low Income	1.05 (0.90-1.23)	1.00 (0.85-1.18)
High Income	0.74 (0.54-1.03)	0.78 (0.56-1.08)
4. Overweight	1.09 (0.92-1.29)	1.06 (0.89-1.26)
5. Obesity	1.32 (1.09-1.59)	1.26 (1.03-1.52)
6. Drinker Category		
Non-drinker	1.21 (1.03-1.43)	1.20 (1.01-1.42)
Heavy Drinker	1.00 (0.74-1.35)	0.98 (0.72-1.33)
7. MRSA	2.33 (1.78-3.05)	2.33 (1.78-3.06)
8. History of Antibiotic Use	1.28 (1.09-1.50)	1.27 (1.08-1.50)

4.3 LACK OF WEIGHT-BASED DOSING AND ATF

For the second thesis objective concerning the association between current dosing practices and ATF, a subgroup analysis involving patients receiving an oral antibiotic at T_0 was performed. The relationship between antibiotic daily dose (DD), BMI and ATF was first explored by plotting the antibiotic DD vs. BMI for patients with and without ATF, where it was shown that DD remained fairly constant with increasing BMI for both groups until BMI reached approximately 40 kg/m^2. Interestingly, although the slope of the regression line for the ATF group was practically parallel to the non-ATF group, it can be seen that the intercept and, therefore, the initial starting antibiotic DD was generally higher for patients who had an episode of treatment failure. Moreover, when BMI reached the morbid obesity range ($\geq$40kg/m^2), the ATF regression line's slope became

increasingly negative, converging onto the non-ATF regression line. Figure 4.4 illustrates the lack of weight-based antibiotic dosing (see below).

Mean DDs were compared between normal, overweight and obese weight groups using Tukey-Kramer adjustments for multiple comparisons. The mean antibiotic DDs for the normal weight, overweight and obese weight classes were 1 051.6 mg/day (95% CI 1 031.1-1 073.2), 1 057.5 mg/day (95% CI 1 035.7-1 079.2), and 1 086.5 mg/day (95% CI 1 056.9-1 116.0), respectively. Although the mean DD for the obese weight group was the highest among weight groups and DD seems to increase with weight category, the difference between DD group means were found to be non-significant (p-value>0.05), confirming findings from the DD vs. BMI plot. DD to BMI group ratio means were also reported and compared in a similar manner; the DD to BMI ratio means decreased with increasing degrees of obesity, where ratio means for normal weight, overweight and obese weight categories were 47.1 (95% CI 46.2-47.9), 38.9 (95% CI 38.0-39.7), and 32.6 (95% CI 31.4-33.8), respectively. Accordingly, the decrease in ratio means for patients with excess weight was found to be statistically significant between weight groups, reflecting a lack of weight-based antibiotic dosing. Table 4.6 presents the DD:BMI ratio means by weight group in addition to the p-values resulting from Tukey-Kramer tests for multiple comparisons.

Table 4.6–Comparison of DD:BMI Ratios between Weight Groups using Tukey-Kramer Tests

Table 4.6 Daily dose (DD) to body max index (BMI) ratio means (LSMEANS) and the difference in ratio means between weight groups (DIFF MEANS) are reported along with 95% confidence intervals. Multiple comparison tests of ratio means between weight groups were performed using the Tukey-Kramer adjustment and resulting p-values are presented on the right. Group 1, group 2 and group 3 represent normal weight, overweight and obese weight classes, respectively.

WEIGHT CATEGORY	DD: BMI RATIO MEANS		P-VALUES		
	DD: BMI LSMEANS (95% CI)	DIFF MEANS (95% CI)	1 vs. 2	1 vs. 3	2 vs. 3
1. Normal Weight	47.1 (46.2-47.9)	8.2 (6.8-9.6)	<0.0001	<0.0001	---
2. Overweight	38.9 (38.0-39.7)	14.4 (12.7-16.2)	<0.0001	---	<0.0001
3. Obese	32.6 (31.4-33.8)	6.3 (4,5-8.0)	---	<0.0001	<0.0001

Figure 4.4–Relationship between Antibiotic DD and BMI for Patients with and without ATF

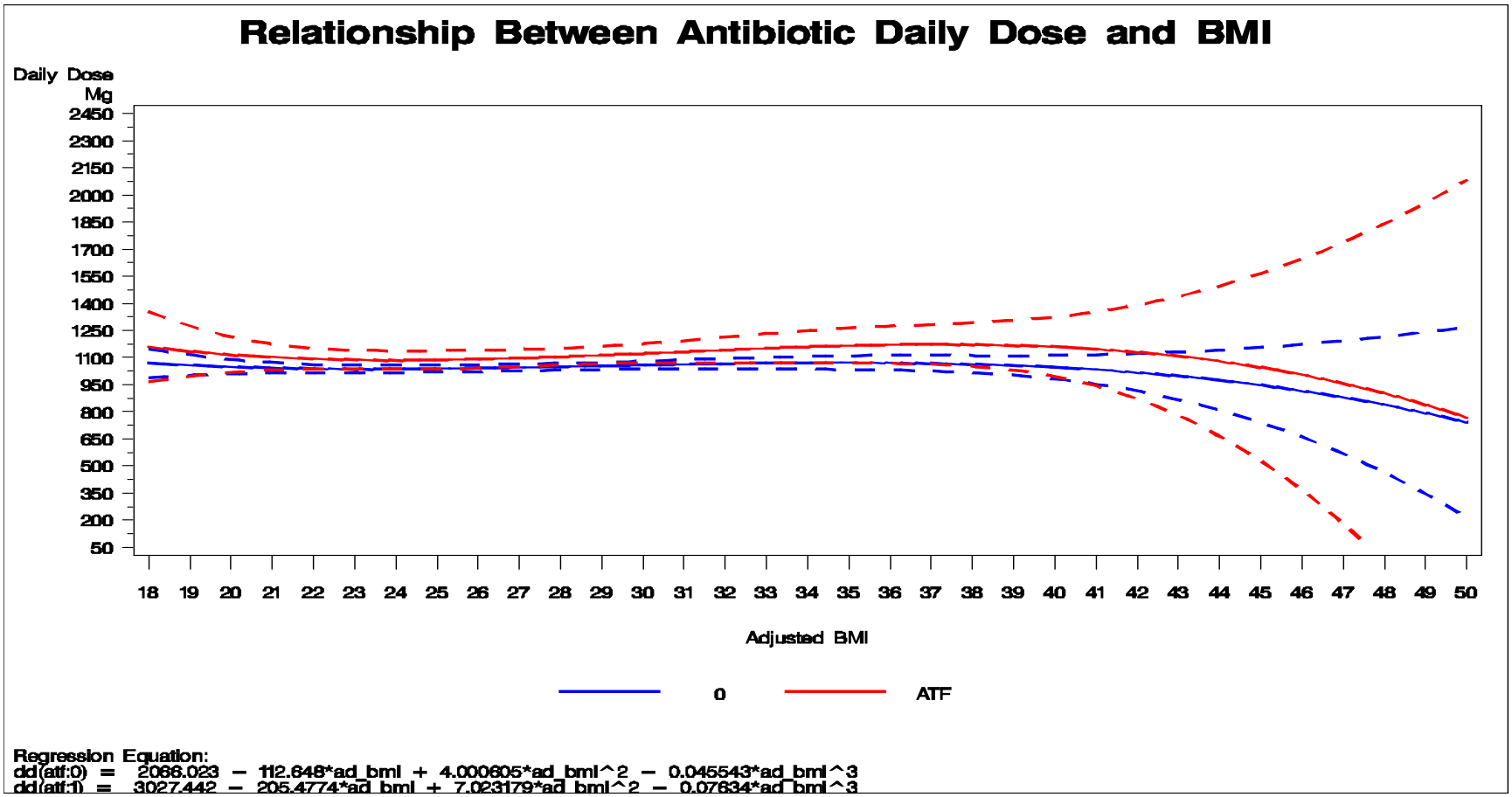


Figure 4.4 The relationship between the initial antibiotic daily dose (DD) at T_0 and the self-reported Body Mass Index (BMI), adjusted for reporting bias at baseline, is displayed in the graph. The outcome group (ATF) is defined by the red regression line.

As part of a secondary logistic regression analysis, additional variables pertaining to antibiotic dosing practices such as DD:BMI and type of antibiotic prescriber (e.g. family physician prescriber vs. others) were included along with previously identified covariates and confounding variables in the final model (i.e. *Model 3*) to determine if dosing factors qualified as statistically significant predictors of ATF. Following stepwise selection, the DD:BMI dosing variable was retained, while type of prescriber did not meet the 0.1 significance level criterion for entry into the final predictive ATF model. DD:BMI was a significant predictor with a corresponding p-value of 0.03, while the crude and adjusted ORs for DD:BMI showed only a 0.5%(OR_{CR} 1.005; 95% CI 1.002-1.009) and 0.4% (OR_{ADJ} 1.004; 95% CI 1.000-1.007) increase in ATF risk, respectively.

5.0 DISCUSSION

5.1 SUMMARY OF MAIN FINDINGS AND COMPARISON WITH EXISTING LITERATURE

Approximately 60% of all study patients aged 20-79 years receiving at least one episode of antibiotic therapy had excess weight, with 39% being overweight and 21% being obese. The observed increase in antibiotic use among these weight groups for our study is likely to be due to the fact that excess weight increases the risk of acquiring infection, particularly lower respiratory tract (e.g. CAP) as well as skin and soft-tissue infections. Prescribing of both broad-spectrum oral antibiotic classes such as penicillins and macrolides as well as broad-spectrum antibacterial medications such as amoxicillin, ciprofloxacin and phenoxymethylpenicillin was quite similar across all weight groups in the primary health care setting.

It is no surprise that the most frequently prescribed oral antibacterial classes in this study have broad-spectrum activity as the 2006 CIPARS report demonstrated similar findings with penicillins (27%), macrolides (23%) and tetracyclines (13%) heading the list of dispense rates in Canada.[45] This increase in broad-spectrum prescribing at the primary care level is thought to be a consequence of the recent reduction in antibiotic prescribing rates as a whole as well as physician uncertainty accompanying whether the suspected underlying infection is due to a gram-positive or gram-negative microorganism, which decreases the probability of failure from inadequate drug coverage.[45, 223-225] Moreover, the most common antibacterial indications for patients with excess weight were lower respiratory tract infections and/or skin and soft tissue infections (SSTIs); these findings were consistent with the scientific literature, since overweight and obese patients have been shown to have an increased risk of community-acquired pneumonia[50] as well as a wide variety of SSTIs such as cellulitis, erypsilas, abscesses and necrotizing fasciitis.[226]

Of the study patients confirmed to have received an oral antibiotic prescription, bacterial infection was coded only a quarter of the time in the

Medical Service Claims database with an overall coding rate of 26.3%. We hypothesized that this striking mismatch between ICD-9 coding within the Medical Service Claims database and the confirmation of receipt of antibacterial medications via the Prescription Claims database be a consequence of coding underlying chronic illnesses (e.g. diabetes) as the primary reason for medical consultation rather than the drug indication. It may also be partially due to a 'delayed prescribing' technique in which primary care physicians issue an antibiotic prescription to the patient on the condition that he/she does not redeem the script unless symptoms fail to improve within the following days. Peterson and Hayward suggest this technique may lead to a modest overestimate of prescribing, which is not possible to measure.[34]

The overall observed antibiotic treatment failure rate for our study was approximately 13% with the outcome occurring more frequently among patients with excess weight than those in the normal weight category, accounting for nearly 64% of antibiotic failures. In contrast to the antibiotic failure rates reported to range from 6% to 35% in the Sanchez-Garcia review article regarding early failure using comparable definitions of ATF,[41, 46, 185, 190] our 13% rate among 6 179 study patients appears to be situated in the middle. Significant predictors of ATF were obesity, SSTI infections typically linked to CA-MRSA, recent history of antibiotic consumption (i.e. in year prior to T_0) as well as non-drinkers. As expected, patients with skin and soft-tissue infections commonly associated with community-acquired MRSA were 133% more likely to have an ATF event and those with a recent history of antibiotic therapy (i.e. within the year prior to T_0) had significantly higher odds of treatment failure (OR_{ADJ} 1.27). We found that obese individuals with infection were 26% more likely to have antibiotic treatment fail than their normal weight counterparts, while overweight individuals had only a 6% increase in treatment failure risk for a variety of acute infections. This may be explicable in terms of antibacterial medication pharmacokinetics known to be considerably altered in patients with excess weight.[5, 13, 36, 108]

Although a substantial amount of evidence exists supporting the association between antibacterial resistance (e.g. MRSA)[41] as well as a recent

history of antibiotic use[142] and the occurrence of ATF, obesity has not yet been documented as an independent risk factor for antibiotic failure. It has, however, been shown to be a strong risk factor for the acquisition of MRSA (both community and hospital acquired),[211] which is a major cause of ATF. Nevertheless, our findings build upon the study conducted by Abdullahi and associates, who have demonstrated an association between BMI and H. pylori eradication success; patients with excess weight had a significantly lower eradication rate in comparison to the control group, while BMI was found to be a significant predictor of H. pylori treatment failure with a corresponding OR of 1.06 (95% CI 1.01-1.11).[143]

In contrast to other studies investigating predictors of ATF,[41] confounding variables such as age, gender, comorbidity, heavy drinking or smoking did not have an effect on odds of ATF. In fact, findings revealed non-drinkers to have a 21% increase in probability of treatment failure. This result was consistent with other research, which have revealed moderate alcohol consumption to have beneficial effects on numerous conditions,[227] while non-drinkers were shown to have a significantly reduced H. pylori eradication rate as compared to drinkers.[228]

The subgroup analysis, which involved the comparison of oral antibiotic daily dose (DD) means as well as daily dose to body mass index ratio (DD:BMI) means between weight groups for infections initially treated at the primary care level, confirmed that current dosing practices do not consider weight as there was no evidence of a dose-response relationship with BMI for both the ATF and non-ATF patient groups. The DD to BMI ratio means dropped in obesity with a mere 32.6 mg/day for each BMI unit, which translates to only 70% of the standard DD to BMI ratio for normal weight patients. Interestingly, the DD vs. BMI plot showed that patients with ATF generally had a higher average initial dose at T_0 when compared to those without ATF. Although both linear regression slopes were nearly equivalent, the ATF regression line began to converge on that of the non-ATF group when BMI reached the morbidly obese range (e.g. $\geq 40 kg/m^2$). This higher initial loading dose for the patients with treatment failure is likely the result of the lack of specificity in antibiotic dosage codes in the Prescription

Claims Database, which tends to contain a wide mg range (e.g. 250mg-800mg) attached to numerous dosing codes; consequently, the highest dose value was selected when faced with a vague range of doses in order to remain conservative with respect to the secondary hypothesis and/or objective (i.e. underdosing of antibiotics in patients with excess weight is associated with ATF). It may also be due to the fact that these patients had a slightly higher incidence of renal/liver disease (1.9% ATF vs. 1.6% non-ATF) and diabetes (8.6% ATF vs. 6.8% non-ATF), which may have led to a higher oral antibiotic dose at T_0. Moreover, the severity of infection (e.g. CAP vs. sinusitis) may have played a role in higher initial antibiotic dosing regimens for patients in the ATF group. At a BMI of approximately 40kg/m^2, the antibiotic DD values began to drop dramatically with higher obesity severity; this decrease is more pronounced in the ATF group as compared to the non-ATF group, which may explain why study results showed that obesity (including morbid obesity) was a significant predictor of antibiotic failure.

The lack of weight-based dosing, reflected by the significant difference in antibiotic DD to BMI ratio means between weight groups along with the increasingly negative relationship between antibiotic DD and BMI for morbidly obese patients with ATF, supports the notion of underdosing or difficulty in attaining therapeutic targets in this patient demographic due to the unfavorable distribution of antibiotic medications in adipose tissue. Although the antibiotic daily dose to BMI ratio variable has a p-value of 0.03 in our secondary logistic regression model, it resulted in a modest 0.4% increase in the odds of antibiotic failure. Possible explanations for this discrepancy is the lack of variation in oral antibiotic dosages, since the same oral doses were repeatedly prescribed; over 50% of patients receiving an oral antibiotic at T_0 had DDs of either 500 mg/day (11%), 1 000 mg/day (20%), 1 500 mg/day (15%) or 1 600 mg/day (8%). Nonetheless, the data indicate that the antibiotic DD:BMI variable was a significant predictor of ATF, which supports the hypothesis that current antibiotic dosing practices may be the culprit of poorer clinical outcomes in obese patients with infections as initially proposed by Falagas and colleagues.[36] Furthermore, the

specialty of the prescribing physician had no effect on the outcome, indicating that current flat-dosing strategies are widespread and part of routine clinical practice.

5.2 STRENGTHS AND LIMITATIONS OF THE STUDY

These data were produced from the first population-based study exploring the relationship between excess weight, dosing practices and antibiotic treatment failure. The linkage of Santé Québec Health Survey data with RAMQ databases, the largest medical data source in the province of Quebec, allowed for the extraction of information on key exposure, confounding and outcome variables. This study provides reason to believe that current antibiotic dosing practices and the increased risk of treatment failure for the obese patient demographic is representative of the Quebec population; the research participants of the 1992 and 1998 Santé Québec Health Surveys who consented to have their health insurance numbers linked to the RAMQ databases as well as the current study sample originating from this data showed a sociodemographic profile similar to all of Quebec.[xv] However, this research project has some limitations. Aside from the obvious drawback of using BMI as a weight descriptor (as stated in Section 3.4.1 "Measures"), other methodological issues include BMI category misclassifications from weight shifts during the course of follow-up as well as difficulty ascertaining cases of antibacterial resistance (e.g. MRSA), inappropriate antibacterial prescribing for suspected viral infections, and/or patient non-compliance to the prescribed antibiotic regimen as plausible causes of ATF, which may have biased the reported association between obesity and treatment failure.

Because weight and height measurements were obtained from the Santé Québec Health Surveys at baseline, it was a challenge to deal with the inherent biases associated with self-reported BMI (i.e. under reporting of weight and the over reporting of height) in addition to the possibility that study participants may have gained or lost weight during the course of follow

[xv] See Appendix 2, Table A2.1 for comparison of sociodemographic variables between groups.

up, which can cause misclassification bias among weight groups.[173] To compensate for this potential misclassification, health survey BMI values were adjusted for reporting bias using a correction regression model developed by Statistics Canada that has been validated to predict an individual's actual BMI from age, sex and self-reported BMI.[182] In order to control for potential weight shifts from the date of the survey until the end of the outcome assessment period, individuals who had any evidence of bariatric surgery and/or pregnancy were excluded from the study population. Because coding of overweight and obesity is not routinely performed by physicians, the RAMQ databases could not be used as a consistent source for updated BMI information during the outcome assessment period. Nevertheless, research suggests there is stability in BMI classification over a 2, 5 and 7-year follow-up range.[229-231] In a prospective population-based study involving 8 548 Canadians, it was found that the majority of participants remained within their WHO defined BMI classification categories over a 5 year time frame. Additionally, when evidence of weight change was present for participants, their BMI class was most likely to have increased, rather than decreased. This weight shift occurred for the normal, overweight and obese weight categories.[231] Therefore, even if a 'natural' weight shift was likely for selected study participants, the resulting weight misclassification would qualify as non-differential as the corresponding change in the exposure variable occurs uniformly within the study population, which draws the measure of effect towards the null value (underestimating the true measure of effect).

Achieving an unbiased association between obesity and antibiotic treatment failure was a complicated task as it is difficult to control for all other potential causes of ATF. Obesity is a known risk factor for MRSA and, therefore, accounting for resistance as a confounder was crucial. Because antibacterial resistance is rarely coded in the MED-ECHO or Medical Service Claims databases as a cause for hospital admission or additional antibiotic prescriptions, respectively, a proxy resistance variable comprising of a

particular subgroup of SSTIs commonly linked to the community-acquired MRSA strain[xvi] and known to occur more frequently among obese patients was created. Moreover, study patients who had a recent history of any type of antibiotic therapy (i.e. within the year preceding T_0) were labeled as potential resistance carriers and were accounted for in the logistic regression analysis. Inappropriate prescribing of antibiotics for suspected viral infections as cause of ATF was also a concern at the primary care level. However, the variable 'flu season', the proxy for inappropriate antibiotic prescribing, was shown to be a non-significant factor in the final predictive model for the outcome, confirming that seasonal variation in ATF rates was not an issue.

As dispensed medications were used to measure antibiotic therapy, we were unable to assess whether patients successfully completed their treatment regimen. Although compliance is a legitimate concern, there is no evidence to suggest a difference in antibiotic noncompliance rates among weight groups. In fact, proven predictors of antibiotic non-adherence include patient health beliefs, doctor-patient relationship and drug regimen.[232] Accordingly, a proportion of ATFs may have occurred as a result of patient noncompliance, but this would be similar within each of the weight classes. Finally, the problem of missing survey information on confounding variables at baseline was also a limitation within the data; however, this was dealt with by placing all missing data on confounding variables into the known outcome risk category – a conservative method of dealing with missing data as this would underestimate the true measure of effect.

Despite these methodological limitations, study results clearly indicate that obesity is significantly associated with antibiotic treatment failure and that current dosing practices are inadequate with increasing degrees of obesity.

[xvi] Please refer to Appendix 2 for the list of SSTIs commonly associated with CA-MRSA

5.3 CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE

In conclusion, alternative antibiotic dosing strategies are likely necessary when treating obese patients for acute infections as a means of reducing the risk of treatment failure. Sufficient pharmacokinetic evidence exists to begin supporting the implementation of weight-based dosing for some of the most commonly prescribed antibiotic medications, while others require further analysis in patients with excess weight. With obesity as a significant predictor of antibiotic treatment failure, establishing obesity-specific guidelines for the management of infections would be the first step towards adopting 'patient-tailored' clinical therapy. Identification of dosage adjustments with respect to body size and composition is needed and should be an integral part of the development process of new antimicrobial medications or clinical trials. Implementation research as a means of ensuring physician adherence to weight-based dosing guidelines that currently exist for aminoglycosides and vancomycin should be encouraged as part of quality assurance programs. Large prospective studies are warranted to investigate the association of weight-based versus standard antibiotic dosing with a clinical outcome as an end point in both primary care and tertiary care settings.

Preventing antibiotic treatment failure can have substantial health care cost benefits. Dosing antibiotics based on weight has the potential to reduce the incidence of antibacterial resistance in patients with excess weight. This study will provide useful information to health care authorities as well as other investigators by encouraging further research in the field of pharmacokinetics in order to find a means of adjusting current antibiotic dosing guidelines for body size and composition characteristics.

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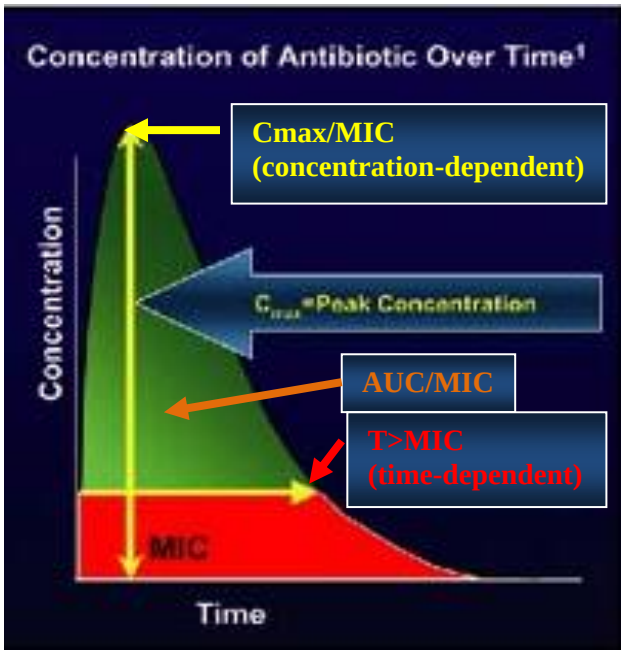
APPENDIX 1

A1. 1 Pharmacodynamics: Antibacterial Mechanisms of Eradication

Bactericidal antibiotics eradicate their target microorganisms via two mechanisms: i) concentration-dependent and/or ii) time-dependent killing; nevertheless, both groups of bactericidal antibiotics rely on surpassing the MIC in order to fully exert their killing properties. While time-dependent agents require concentrations 4 to 5 times the MIC, concentration-dependent antibiotics necessitate peak levels of 8 to 10 times that of the MIC.[97] With respect to concentration-dependent agents, the ratio of the peak antibiotic concentration to the MIC (Cmax: MIC) as well as the ratio of the area under the serum concentration-time curve to the MIC (AUC: MIC) are important indices that reflect antimicrobial efficacy. Conversely, the efficacy of time-dependent antibiotics may be predicted by the percentage of time within a dosage interval where the drug concentrations exceed that of the bacteria's MIC (T>MIC). Moreover, bacteriostatic agents are generally thought to be time-dependent as well, with the exception of particular antibiotics that may benefit from an increase in the total drug exposure (i.e. the AUC). The figure below depicts the pharmacodynamic indices that are thought to best predict antibiotic efficacy and, thus, the attainment of therapeutic targets.[5]

Figure A1.1–The Concentration vs. Time Curve and Important Pharmacodynamic Indices for Antibacterial Agents[233]



A1.2 Other Possible Causes of Antibiotic Treatment Failure

A1.2.1 Inappropriate Use for Infections Not Susceptible to Antibiotic Treatment

Until recently, it was common practice to prescribe antibiotics to patients with suspected viral infections in order to improve symptoms. Cadieux and colleagues reported that inappropriate prescribing of antibiotics for respiratory viral infections varied by diagnosis and ranged from 22% for laryngitis to 43% for influenza cases in Quebec from 1990-1998.[234] With the emergence and rise of various multiple-resistant bacterial strains by 1995, researchers urged physicians, particularly those in primary care, to restrain from issuing antibiotics for common infections that are most likely of viral origin after proving that antibiotics have little therapeutic benefit for such infections. Accordingly, new prescribing standards and implementation strategies were developed as a means of reducing unnecessary antibiotic prescribing as well as overall antibiotic prescribing rates.[223] This attention and awareness to inappropriate practices among physicians was subsequently followed by a significant decrease in primary care antibiotic prescribing rates in most developed countries, including the United States and Canada. [45, 223-225] For instance, the consumption and prescription rates for oral, solid and liquid antimicrobials in Canada decreased by 11% and 29.8% between 1995 and 2000, respectively.[136]

Factors shown to predict inappropriate antibiotic prescribing practices among physicians include physician-patient interaction variables (e.g. pressure exerted by the patient on the physician),[235-237] physician characteristics (e.g. international medical graduates, practice experience, male gender, high practice volume)[238-241] as well as difficulty distinguishing a benign viral infection from a more serious bacterial infection in adult patients who have contracted pharyngtis,[242] sinusitis,[243] and bronchitis.[243-244] Aside from the severity of infection, there is no evidence to suggest that patient characteristics, including body mass index, affects the appropriateness of antibacterial prescribing practices in primary care.[245]

A1.2.2 Wrong Choice of Antibiotic

In addition to unnecessarily prescribing antibiotics for infections of suspected viral origin, inadequate drug coverage from the selection of antibacterial medications with too narrow of a spectrum activity against their corresponding bacteria also constitutes one of the main causes for the occurrence of ATF.[41] Although the wrong choice of antibiotic is a valid concern, statistics indicate that a significant increase in consumption and dispensing of broad-spectrum antibiotics to patients with infections had accompanied the reduction in overall antimicrobial prescribing rates in Canada (as described previously).[225] The 2006 CIPARS report revealed extended-spectrum penicillins (27%), macrolides (23%) and tetracylines (13%) as the most frequently dispensed oral antibiotic classes, which all have broad-spectrum activity.[45] Thus, the uncertainty of determining whether the underlying infection is due to gram-positive or gram-negative bacteria had led primary care physicians to select antibacterial medications with broad-spectrums and, in turn, decreasing the probability of failure from inadequate coverage.

A study evaluating the predictors of broad-spectrum antibiotic prescribing for adults with acute respiratory tract infections in the primary care setting found that physician specialty and geographic region of practice had a significant influence on prescribing practice; internal medicine physicians were more likely to choose broad-spectrum antibiotics over narrow-spectrum than general practitioners as well as those practicing in Northeastern United States as compared to the South. Certain patient characteristics were also found to influence broad-spectrum antibiotic prescription rates; black ethnicity, lack of health insurance, and health maintenance organization memberships were associated with lower broad-spectrum prescribing rates, while patient age, sex and urban versus rural location were not associated with prescribing choice. A patient's weight was not shown to influence antibiotic choice.[246]

A1.2.3 Patient Non-Compliance with Medication Regimen

Patient non-compliance with the prescribed antibacterial medication regimen is known to be strongly linked with treatment failure and its associated consequences (e.g. deterioration of health, additional physician visits, consumption of additional drugs as well as increases in hospital admission rates). Non-compliance rates have been reported to reach up to 30%.[247, 248] Despite the perception of medication non-compliance occurring most frequently among patients with chronic conditions,[135] it was shown that the compliance of patients with acute respiratory tract infections is not ideal. Favre and colleagues measured compliance with an antibiotic regimen using Medication Event Monitoring System (MEMS) technology, which records each opening of the pill bottle and assumes this as the equivalent of a presumptive dose. The "taking compliance," defined as the ratio of the total number of times the bottle was opened to the total number of prescribed doses during the period of monitoring, was found to be almost perfect with a 99.6% adherence rate. Although only one third of all medications were taken according to the recommended time intervals between two consecutive doses, the authors concluded that patients receiving antibiotics twice daily usually comply with the prescribed therapy.[42]

Proven predictors of non-compliance to prescribed antibiotic regimens include patient health beliefs, physician characteristics (e.g. age and years in practice) doctor-patient relationship variables (e.g. patient's attitude towards the consultation, knowing the consulting physician well etc.) as well as the length and complexity of the drug regimen.[232] Of these, the complexity of the prescribed drug regimen seems to have the most significant influence on patient compliance, specifically with respect to treatment for respiratory infections, where once daily antibiotic dosing regimens had considerably higher patient compliance rates than twice, three or four times daily dosing regimens.[135, 249] Patient characteristics such as age, employment state or low income and perception of health status (i.e. perceiving the condition as not severe) were found to be positively correlated with medication non-

compliance, while other variables were found to have no influence.[232] Body mass index is not a known predictor of patient noncompliance with antibiotic medications.

Table A1.1-Key Characteristics of Commonly Prescribed Antibiotic Medication Classes in Primary Care[126]

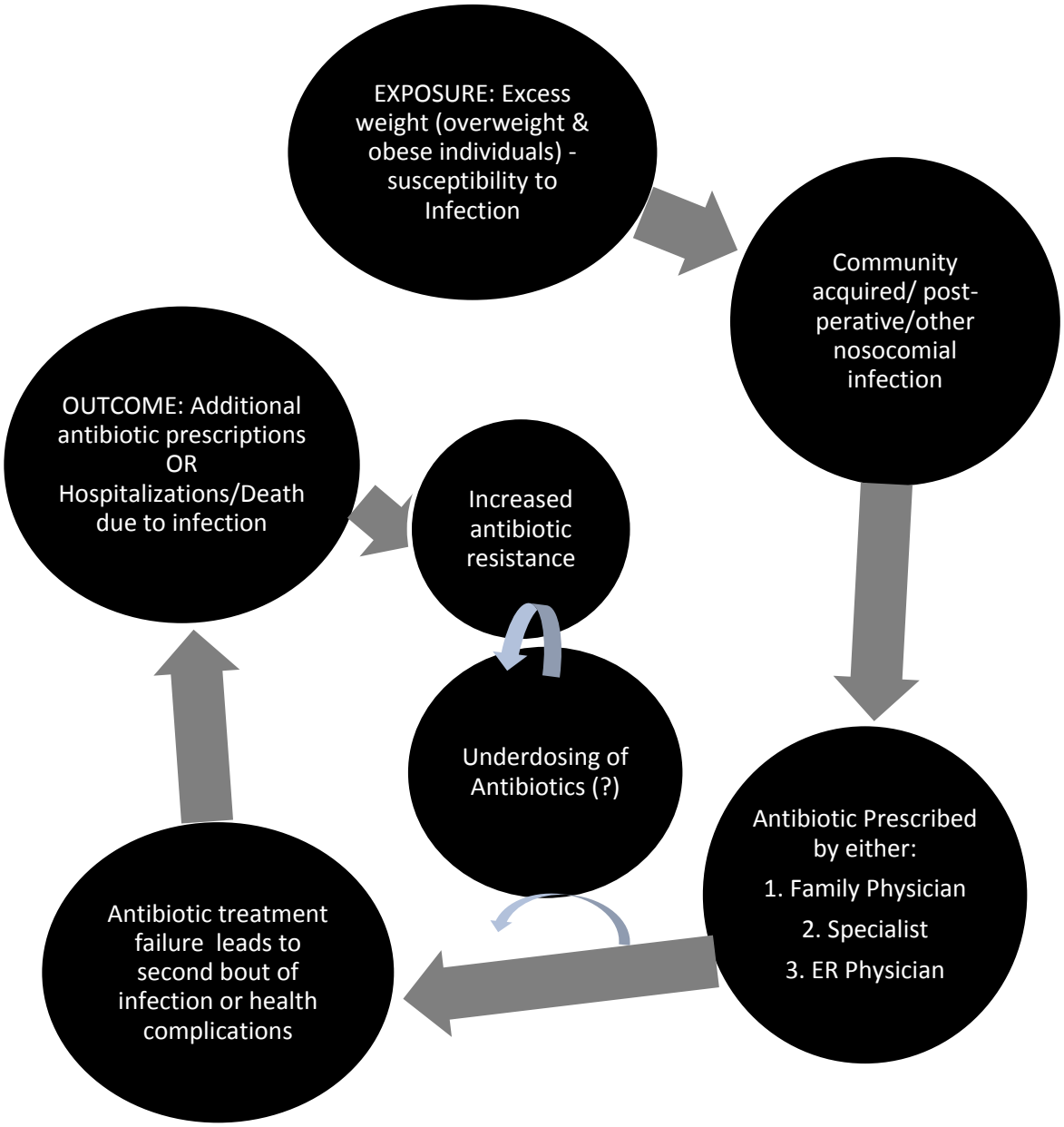
ANTIBIOTIC CLASS	PRIMARY INDICATION	TYPE OF PHARMACOLOGIC ACTIVITY	DOSING CONSIDERATIONS	EXAMPLES
AMINOGLYCOSIDES	Gram – bacillary infections (e.g. enterococcal endocarditis)	Concentration-dependent bactericidal	Loading IV dose is weight-based (mg/kg) Maintenance dose is adjusted for renal function	Tobramycin Neomycin Kanamycin
FLUOROQUINOLONES	Broad spectrum (e.g. UTIs, CAP, HAP, salmonella)	Concentration-dependent bactericidal	Dosing adjustments only for patients with renal insufficiency	Ciprofloxacin
B-LACTAMS **Cephalosporins** **Penicillins**	Broad-spectrum (e.g. UTIs, meningitis, RTIs, enterococcal infections)	Time-dependent bactericidal	Dosing adjustments only made for patients with renal insufficiency	Amoxicillin Phenoxymethyl -penicillin Ampicillin
MACROLIDES	Gram + bacteria (e.g. RTIs and SSTIs)	Time-dependent bacteriostatic	None	Erythromycin Clarithromycin Azithromycin
TETRACYCLINES	Broad spectrum (e.g. bacterial-resistant infections)	Time-dependent bacteriostatic	None	Doxycycline Hyclate Tetracycline Hydrochloride
SULFONAMIDES	Broad-spectrum (e.g. nocardiosis, UTIs)	Time-dependent bacteriostatic	Loading IV doses is weight-based, but no such adjustment exists for the oral tablet form	Sulfacetamide Trimethoprim/ Sulfamethoxazole
LINCOSAMIDES	Broad-spectrum (e.g. SSTIs, anaerobic bacteria,)	Time-dependent bacteriostatic	None	Clindamycin
OXAZOLIDINONE	Broad-spectrum (e.g. SSTIs, CAP)	Time-dependent bacteriostatic + bactericidal	None	Linezolid
OTHER ANGENTS **Nitrofurantoin**	Narrow-spectrum (e.g. Uropathogens – uncomplicated UTIs)	Bactericidal	None	Furadantin, Macrobid, Macrodantin

Table A1.2–Clinical Criteria for ATF Detection [41, 46, 185-186, 188, 190-191, 193]

Table A1.2 was adapted from Sanchez-Garcia (2009)[41] Early death, additional antibiotic or change in regimen as well as admission to an acute care hospital facility were used to define antibiotic treatment failure.

CRITERIA	VARIABLES
Patient-based	Early Death*
1. Physical Examination	Persistent fever >38°C or hypothermia, increased heart rate, respiratory rate > 25/min, cough, expectoration, purulent bronchial secretions, dyspnea, hypotension, altered mental status, malaise
2. Organ Dysfunction	Acute respiratory failure (partial arterial oxygen pressure < 55 mmHg or worsening PaO2/FiO2 ratio, peripheral oxygen saturation < 90%), hypotension, septic shock, multiple organ dysfunction syndrome.
Treatment-based	
1. Antibiotic therapy	Additional antibiotic or change in regimen*
2. Admission to ICU*	
3. Organ support	Vasopressor drugs, mechanical ventilation
4. Surgery	Need for re-operation: debridement or re-laparotomy
Test-based	
1. Microbiological In vitro resistance Polymicrobial Persistence	Minimal inhibitory concentration
2. Laboratory test	Leucocytes, neutrophils, blood urea nitrogen, glucose, sodium, hematocrit, C-reactive protein, procalcitonin
3. Chest Radiograph	Sequential assessment of infiltrate: slowly resolving, persistence, progression

Figure A1.2–Theoretical Model Linking Excess Weight to Antibiotic Treatment Failure



APPENDIX 2

Table A2.1- Representativeness of Study Population

VARIABLES	POPULATION-BASED HEALTH SURVEY*		RAMQ COHORT (N= 17 826)	STUDY COHORT (N= 6 179)
	1992-1993 (%)	1998 (%)		
Gender				
Female	50.4	50.9	9 636 (54.1)	3 453 (55.9)
Age				
<65	89.7	88.6	15 568 (87.3)	3 902 (63.1)
65+	10.3	11.4	2 048 (12.7)	2 277 (36.9)
SES				
Low Income	20.2	19.4	3 627 (20.4)	2 047 (33.1)
Middle Income	67.7	69.3	12 227 (68.6)	3 706 (60.0)
High Income	12.1	11.3	1 972 (11.1)	426 (6.9)
BMI				
Underweight	10.8	13.1	804 (4.5)	.
Normal Weight	62.8	57.2	8 384 (47.0)	2 444 (39.6)
Excess Weight	24.1	27.4	8 638 (45.8)	3 735 (60.5)
Missing	2.3	2.3	485 (2.7)	.
Smoking				
Never	31.7	32.4	4 887 (27.9)	1 575 (25.5)
Current-Ever	68.3	67.6	12 939 (72.1)	4 604 (74.5)
Drinking				
Non-Drinkers	21.5	18.7	3 508 (19.7)	1 746 (28.3)
Drinkers	78.5	81.3	14 318 (80.3)	4 433 (71.7)

*Health survey data is a weighted percentage of the Quebec population

Table A2.2 – List of Acute and Non-Acute Infections Requiring Antibiotic Therapy

DISEASE INDEX	SUBSECTION DESCRIPTION	ICD-9 CODES	ICD-9 SUBCLASS	DESCRIPTION	DEFINITION OF CONDITIONS/ ANTIBIOTIC TREATMENTS*
POSSIBLE INFECTIONS					
Infectious & Parasitic Diseases (001-139)	Intestinal infectious diseases (001-009): Typhoid and Paratyphoid fevers	002	002.0	Typhoid fever	Paratyphoid fevers or Enteric fevers are a group of enteric illnesses caused by strains of the bacterium *Salmonella paratyphi*. Antibiotics such as Azithromycin are particularly effective in treating the bacteria and this course is usually given for **14 days**.
			002.1	Paratyphoid fever A	
			002.2	Paratyphoid fever B	
			002.3	Paratyphoid fever C	
			002.9	Paratyphoid fever, unspecified	
Infectious & Parasitic Diseases (001-139)	Intestinal infectious diseases (001-009): other salmonella infections	003	003.0	Salmonella gastroenteritis (salmonellosis)	Salmonellosis is an infection with *Salmonella* bacteria. In most cases, the illness lasts **4 to 7 days** and most people recover without treatment. In severe cases, the *Salmonella* infection may spread from the intestines to the blood stream or other body sites and can cause death unless the person is treated promptly with antibiotics. Bacteremia and focal infections may require antibiotics for up to **4 to 6 weeks** depending on the site of infection and serotype of *Salmonella.*
			003.1	Salmonella septicemia (complications)	
			003.2	Localized salmonella infections (complications): 003.21 Salmonella meningitis 003.22 Salmonella pneumonia 003.23 Salmonella arthritis 003.24 Salmonella osteomyelitis 003.29 Other	
			003.8	Other specified salmonella infections	
			003.9	Salmonella infection, unspecified	
Infectious & Parasitic Diseases (001-139)	Intestinal infectious diseases (001-009)	004	004	Shigellosis	Shigellosis is an acute bacterial infection of the lining of the intestines. Antibiotics can help shorten the length of the illness. Frequently used antibiotics include sulfamethoxazole-trimethoprim (Bactrim), ampicillin, ciprofloxacin (Cipro), or azithromycin. In most cases,

					the disease resolves within **4 to 8 days** without antibiotics. Severe infections may last 3-6 weeks.
		006	006	Amebiasis	Amebiasis is an infection of the intestines caused by the parasite *Entamoeba histolytica.* Treatment depends on the severity of infection. Usually, metronidaloze is given by mouth for **10 days.**
Infectious & Parasitic Diseases (001-139)	Intestinal infectious diseases(001-009)	007	007.0	Balantidiasis	Balantidiasis is a protozoal infection. Treatment can consist of antibiotics for **10 days.**
			007.3	Intestinal trichomoniasis	Trichomoniasis is an intestinal protozoal infection. Metronidazole is highly effective against trichomoniasis. Either a single two gram dose (85-92% cure rate) or 250 mg three time daily for **7 to 10 days** (>95% cure rate) can be used.
			007.5	Cyclosporiasis	Cyclosporiasis is an intestinal protozoal infection. TMP-SMZ is the drug of choice and the oral drug course ranges from **7 to 10 days**.
Infectious & Parasitic Diseases (001-139)	Intestinal infectious diseases(001-009): intestinal infections due to other organisms	008	008.0	E. coli	*E. coli* are extremely sensitive to such antibiotics as streptomycin or gentamicin. Length of treatment depends heavily upon the type of E. coli infection.
			008.1	Arizona group of paracolon bacilli	
			008.2	Aerobacter aerogenes – enterobacter aerogenes	With few exceptions, the major classes of antibiotics used to manage infections with these bacteria include the beta-lactams, the fluoroquinolones, the aminoglycosides, and TMP-SMZ.

			008.3	Proteus mirabillis	Proteus species are part of the Enterobacteria family of gram-negative bacilli, which commonly cause UTIs. *P. mirabilis* is generally susceptible to most antibiotics apart from tetracycline. Treatment lasts anywhere from **3 to 21 days**.
			008.4	Other specified bacteria: 008.41 Staphylococcus Staphylococcal enterocolitis 008.42 Pseudomonas 008.43 Campylobacter 008.44 Yersinia enterocolitica 008.45 Clostridium difficile Pseudomembranous colitis 008.46 Other anaerobes Anaerobic enteritis NOS Bacteroides (fragilis) Gram-negative anaerobes 008.47 Other gram-negative bacteria Gram-negative enteritis NOS	
			008.5	Bacterial enteritis, unspecified	
Infectious & Parasitic Diseases (001-139)	Intestinal infectious diseases: ill-defined intestinal infections	009	009.0	Infectious colitis, enteritis, and gastroenteritis	A well-known subtype of infectious colitis is pseudomembranous colitis, which results from infection by a toxigenic (produces toxins) strain of *Clostridium difficile* (c-diff). It is treated with antibiotics and duration ranges from **10to 14 days**.
			009.1	Colitis, enteritis, and gastroenteritis of presumed infectious origin	
			009.2	Infectious diarrhea	
			009.3	Diarrhea of presumed infectious origin	

Infectious & Parasitic Diseases (001-139)	Zoonotic bacterial diseases	020-027	021	Tularemia	The drug of choice is Streptomycin. Tularemia may also be treated with gentamicin for **10 days**, tetracycline-class drugs such as doxycycline for **2 to 3 weeks**.
			026	Rat-bite fever	Rat-bite fever is treated with antibiotics. Your health care provider may prescribe penicillin or tetracyclines for **7 to 14 days.**
			027.1	Erysipelothrix infection	An infectious disease caused by the widespread bacterium *Erysipelothrix rhusiopathiae.* Antibiotic therapy for **7-10 days** will usually clear the infection.
Infectious & Parasitic Diseases (001-139)	Other bacterial diseases (030-041)	032	032.0-032.9	Diphteria	Erythromycin (orally or by injection) for **14 days** (40 mg/kg per day with a maximum of 2 g/d).
Infectious & Parasitic Diseases (001-139)	Other bacterial diseases (031-041)	033	033.0-033.9	Whooping cough	It is normal practice to use a **7 day course** of the antibiotic, but some authorities recommend two weeks and others **10 days**.
Infectious & Parasitic Diseases	Other bacterial diseases (030-041)	034	034.0	Streptococcal sore throat	Streptococcal pharyngitis or streptococcal sore throat is a form of group A streptococcal infection that affects the pharynx and possibly the larynx. Treatment with antibiotics for **10 days** is recommended and usually shortens the course of the infection.
			034.1	Scarlet fever	Scarlet fever is a disease caused by exotoxin released by *Streptococcus pyogenes*. Treatment is aimed at providing adequate antistreptococcal antibiotic levels for at least **10 days.**
Infectious & Parasitic Diseases	Other bacterial diseases (030-	035	035	Erysipelas	Erysipelas is an acute streptococcus bacterial infection of the dermis, resulting

	041)				in inflammation. Depending on the severity, treatment involves either oral or intravenous antibiotics, using penicillins, clindamycin or erythromycin. Penicillin administered orally or intramuscularly is sufficient for most cases of classic erysipelas and should be given for **10 to 20 days.**
Infectious & Parasitic Diseases	Other bacterial diseases (030-041)	036	036	Meningococcal infection	Meningococcal bloodstream infections (known as meningococcemia) can range in severity from a transient bacteremia that is relatively benign to an overwhelming infection that is rapidly fatal. Treatment begins with large doses of aqueous penicillin G, ampicillin, or a cephalosporin. Most patients with uncomplicated meningococcemia defervesce within the first 24 hours of antibiotic therapy. Antibiotic therapy for uncomplicated meningococcemia needs to be administered for only **4 to 5 days** after defervescence occurs, and, in adults, the dosage needed to complete the course of therapy can be reduced. Treatment can range up to **10 days**.
Infectious & Parasitic Diseases	Other bacterial diseases (030-041)	037-040	037	Tetanus	Tetanus is a medical condition characterized by a prolonged contraction of skeletal muscle fibers caused by tetanospasmin, a neurotoxin produced by the Gram-positive, obligate anaerobic bacterium *Clostridium tetani*. Treated with IV antibiotics for **10 to 14 days**

			038	Septicemia (complications)	Septicemia is the presence of bacteria in the blood and is often associated with severe infections. Antimicrobial therapy can range from **3-5 weeks**.
			040.0, 040.1, 40.3, 040.8	040.0 – Gas gangrene (complications) 040.1 – Rhinoscleroma 040.3 – Necrobacillosis 040.8 – Other specified bacterial diseases	Gas gangrene antibiotic therapy ranges from **7-28 days**. Rhinoscleroma antibiotic treatment typically lasts for **7 to 14 days**.
Infectious & Parasitic Diseases	Other bacterial diseases (030-041): bacterial infection in conditions classified elsewhere and of unspecified site	041	041.0	Streptococcus infection in conditions classified elsewhere and of unspecified site	Once group A streptococcus is documented as the cause of infection, treatment with penicillin should be started. Erythromycin or another macrolide can be used in patients who are allergic to penicillin. Treatment with ampicillin/sulbactam is appropriate if deep oropharyngeal abscesses are present. In cases of streptococcal toxic shock syndrome, treatment consists of penicillin and clindamycin, in conjunction with intravenous immunoglobulin. A **10-day course** of penicillin V 500 mg bid or 250 mg qid in adults is very effective.
			041.00	Streptococcus infection in conditions classified elsewhere and of unspecified site – streptococcus unspecified	
			041.01	Streptococcus infection in conditions classified elsewhere and of unspecified site – streptococcus group a	
			041.02	Streptococcus infection in conditions classified elsewhere and of unspecified site – streptococcus group b	
			041.03	Streptococcus infection in conditions classified elsewhere and of unspecified site – streptococcus group c	
			041.04	Streptococcus infection in conditions classified elsewhere and of unspecified site – streptococcus group d (enterococcus)	
			041.05	Streptococcus infection in conditions classified elsewhere and of unspecified site – streptococcus group g	
			041.09	Streptococcus infection in conditions classified elsewhere and of unspecified site – other streptococcus	

	041.1	Staphylococcus infection in conditions classified elsewhere and of unspecified site	The treatment of choice for *S. aureus* infection is penicillin; but, in most countries, penicillin-resistance is extremely common and first-line therapy is most commonly a penicillinase-resistant β-lactam antibiotic (e.g. oxacillin or flucloxacillin). Combination therapy with gentamicin may be used to treat serious infections like endocarditis.
	041.10	Staphylococcus infection in conditions classified elsewhere and of unspecified site-staphylococcus unspecified	
	041.11	Methicillin susceptible staphylococcus aureus	
	041.12	MRSA	
	041.19	Staphylococcus infection	
	041.2	Pneumococcus infection	Historically, treatment relied primarily on β-lactam antibiotics. In the 1960s, nearly all strains of *S. pneumoniae* were susceptible to penicillin, but since that time, there has been an increasing prevalence of penicillin resistance, especially in areas of high antibiotic use. A varying proportion of strains may also be resistant to cephalosporins, macrolides (such as erythromycin), tetracycline, clindamycin and the quinolones.
	041.3	Klebsiella pneumoniae	Agents with high intrinsic activity against *K pneumoniae* should be selected for severely ill patients. Examples of such agents include third-generation cephalosporins (eg, cefotaxime, ceftriaxone), carbapenems (eg, imipenem/cilastatin), aminoglycosides (eg, gentamicin, amikacin), and quinolones.
	041.4	Escherichia coli infection	
	041.5	Hemophilus Influenzae infection	
	041.6	Proteus infection	Uncomplicated UTIs in women can be treated on an outpatient basis with an oral

			quinolone for **3 days** or trimethoprim /sulfamethoxazole (TMP/SMZ) for 3 days. Acute uncomplicated pyelonephritis in women can be treated with oral quinolones for **7 to 14 days**, single-dose ceftriaxone or gentamicin followed by TMP/SMZ, or an oral cephalosporin or quinolone for 14 days as outpatient therapy. Complicated UTIs in men and women can be treated with a **10 to 21 day** course of oral therapy.
	041.7	Pseudomonas infection	Antimicrobial agents are needed to treat *Pseudomonas* infections. Two antipseudomonal drug combination therapies is usually recommended for the initial empiric treatment of a pseudomonal infection, especially for patients with neutropenia, bacteremia, sepsis, severe upper respiratory infections (URIs), or abscess formation.
	041.8	Other specified bacterial infections: 041.81 – mycoplasma 041.82 – bacteroides fragilis 041.83 – Clostridium perfringens 041.84 – anaerobes 041.85 – Other gram –ve organisms 041.86 – H. pylori 041.89 – Other specified bacteria	
	041.9	Bacterial infection, unspecified	

Infectious & Parasitic Diseases	Other Diseases Due to Viruses and Chlamydia (070-079)	073	073	Ornithosis	This infection is treated with antibiotics. Tetracyclines and chloramphenicol are the drugs of choice for treating patients with psittacosis. Treating patients for **2 to 3 weeks** usually prevents relapse. Clinical response occurs within 24-72 hours.
Infectious & Parasitic Diseases	Other Diseases Due to Viruses and Chlamydia (070-079)	077	077.0	Inclusion conjunctivitis	In adults, tetracycline ointment or drops should be applied to the conjunctiva and oral tetracycline, amoxacillin, or erythromycin should be taken for **3 weeks**, or doxycycline for **1 week.**
Infectious & Parasitic Diseases	Rickettsioses and other anthropod-borne diseases (080-088)	080-083, 087	080	Epidemic typhus	Epidemic typhus is caused by Rickettsia prowazekii. Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves and has been afebrile for 24 to 48 h but continued for at least **7 days**. Chloramphenicol 500 mg po or IV qid for **7 days** is 2nd-line treatment.
			081	Other typhus Includes: Murine, scrub and unspecified typhus	**7 days** of antibiotic treatment is usually effective.
			082	Tick-borne rickettsioses	Treatment is with antibiotics for approximately **2 weeks**.
			083	Other rickettsioses	
			087	Relapsing fever	Treated with antibiotics for a course of **7 to 10 days**
Infectious & Parasitic Diseases	Syphilis and Other Venereal Diseases (090-099)	090-099	090	Congenital syphilis	Primary or secondary syphilis - Benzathine penicillin G 2.4 million units IM in a single dose. Early latent syphilis - Benzathine penicillin G 2.4 million units IM in a single dose. Late latent syphilis or latent syphilis of unknown duration - Benzathine penicillin G 7.2 million units
			091	Early syphilis, symptomatic	
			092	Early syphilis, latent	
			093	Cardiovascular syphilis	
			094	Nurosyphilis	

					total, administered as 3 doses of 2.4 million units IM each at **1-week intervals (3 weeks in all)**
			095	Other forms of late syphilis, with symptoms	*Neisseria gonorrhoeae* is responsible for the sexually transmitted infection gonorrhea. Single-dose azithromycin (1g PO) or a 7-day course of doxycycline (100 mg 2 times/day) as empiric treatment is recommended with the cephalosporin therapy for gonorrhea. Tretament can range from **7 to 14 days**.
			096	Late syphilis, latent	
			097	Other and unspecified syphilis	
			098	Gonococcal Infections	
			099	Other venereal diseases	
Infectious & Parasitic Diseases	Other spirochetal diseases (100-104)	100-104	100	Leptospirosis	Leptospirosis is a worldwide zoonosis caused by pathogenic species of the genus *Leptospira.* It is treated with oral antibiotics for **7 days**.
			101	Vincent's angina or ulcerative gingivitis	Marked improvement usually occurs within 24 to 48 h, after which debridement can be completed. If debridement is delayed, oral antibiotics provide rapid relief and can be continued until 72 h after symptoms resolve. Total treatment duration is approximately **5 days**.
			102	Yaws	Yaws is a common chronic infectious disease that occurs mainly in warm humid regions such as the tropical areas of Africa, Asia, South and Central Americas, plus the Pacific Islands. Penicillin G benzathine given IM (intramuscularly) can cure the disease in the primary, secondary, and usually in the latent phase. Penicillin V can be given orally for about **7 to 10 days**, but this route is less reliable than direct

					injection.
			103	Pinta	Pinta is an endemic treponematosis caused by *Treponema carateum.* It is treated with antibiotics for **15 days.**
			104	Other spirochetal infections	
Endocrine, Nutritional and Metabolic Diseases (240-279)	Diseases of the Thyroid Gland (240-246)	245	245.0	Acute thyroiditis: Abscess of thyroid Thyroiditis: nonsuppurative , pyogenic, suppurative	Acute thyroiditis requires immediate parenteral antibiotic therapy before abscess formation begins. Penicillin or ampicillin are administered to cover gram-positive cocci and the anaerobes that are the usual causes of the disease
Endocrine, Nutritional and Metabolic Diseases (240-279)	Diseases of the Thymus Gland (249-259)	254	254.1	Abscess of thymus	Drained and treated with penicillin. The predicted outcome is complete healing within **10 to 14 days**.
Diseases of the Nervous System and Sense Organs (320-389)	Inflammatory Diseases of the Central Nervous System (320 – 326): Bacterial meningitis	320	320.0	Hemophilus meningitis	Antibiotic therapy should be started as soon as possible. Ceftriaxone is one of the most commonly used antibiotics. If the antibiotic is not working, and the health care provider suspects antibiotic resistance, vancomycin or rifampin are used. Treatment duration can range from **7 to 21 days** depending on the causal organism.
			320.1	Pneumococcal meningitis	
			320.2	Streptococcal meningitis	
			320.3	Staphylococcal meningitis	
			320.7	Meningitis in bacterial diseases classified elsewhere	
			320.8	Meningitis due to other specified bacteria	
			320.9	Meningitis due to unspecified bacterium	
Diseases of the Nervous System and Sense Organs (320-389)	Inflammatory Diseases of the Central Nervous System (320–326): Intracranial and intraspinal abscess	324	324.0	Intracranial abscess (complications)	Treatment includes intravenous antibiotics, and/or surgery to drain the infection. Once an abscess has formed, surgical excision or drainage combined with prolonged antibiotics (usually **4 to 8 wk**) remains the treatment of choice.
			324.1	Intraspinal abscess (complications)	
			324.9	Of unspecified site (complications)	

Diseases of the Nervous System and Sense Organs (320-389)	Disorders of the Eye and Adnexa (360 – 379): Disorders of the Globe	360	360.0	Purulent Endophthalmitis 360.00 Purulent endophthalmitis, unspecified 360.01 Acute endophthalmitis 360.02 Panophthalmitis 360.03 Chronic endophtalmitis 360.04 Vitreous abscess	Endophthalmitis is an inflammatory condition of the intraocular cavities (ie, the aqueous or vitreous humor) usually caused by infection. Broad-spectrum intravenous antibiotics including vancomycin and an aminoglycoside or third-generation cephalosporin.
Diseases of the Nervous System and Sense Organs (320-389)	Disorders of the Eye and Adnexa (360 – 379): Keratitis	370	370.0	Corneal ulcer	Bacterial corneal ulcer requires intensive fortified antibiotic therapy to treat the infection. Systemic intravenous antibiotics should be started once an infected corneal ulcer has perforated and for 3 days following the PK. Treatment can range from **3 to 7 days**.
			370.2	Superficial keratitis without conjunctivitis	
			370.3	Certain types of keratoconjunctivitis	
			370.4	Other and unspecified keratoconjunctivitis	
			370.5	Interstitial and deep keratitis	
			370.8	Other forms of keratitis	
			370.9	Unspecified keratitis	
Diseases of the Nervous System and Sense Organs	Disorders of the Eye and Adnexa (360 – 379): Disorders of the Conjunctiva	372	372.0	Acute conjunctivitis: 372.00 Acute conjunctivitis, unspecified 372.01 Serous conjunctivitis, except viral	Bacterial conjunctivitis usually resolves without treatment. Antibiotics, eye drops, or ointment are thus only needed if no improvement is observed after 3 days. In patients receiving no antibiotics recovery was in 4.8 days, immediate antibiotics **3.3 days**, delayed antibiotics 3.9 days.
			372.1	Chronic conjunctivitis: (complications) 372.10 Chronic conjunctivitis, unspecified 372.11 Simple chronic conjunctivitis 372.12 Chronic follicular conjunctivitis 372.13 Vernal conjunctivitis 372.14 Other chronic allergic conjunctivitis 372.15 Parasitic conjunctivitis	Treatment might include antibiotics, artificial tears and other topical medications. Sometimes antibiotics by mouth may be needed. For individual or sporadic cases, azithromycin 20 mg/kg (maximum 1 g) po as a single dose is 78% effective. Alternatives are doxycycline 100 mg bid or tetracycline 250 mg qid for **4 weeks**.

			372.2	Blepharoconjunctivitis	Antibacterial medications usually suffice to treat the bacteria that cause the infection. The medication is typically in the form of eyedrops, but is also available in a topical version.
Diseases of the Nervous System and Sense Organs	Disorders of the Eye and Adnexa (360-379): Inflammation of the eyelids	373	373.1	373.11 Hordeolum externum Hordeolum NOS Stye 373.12 Hordeolum internum Infection of meibomian gland 373.13 Abscess of eyelid Furuncle of eyelid	An external stye or hordeolum is an infection of the sebaceous glands of Zeis at the base of the eyelashes, or an infection of the apocrine sweat glands of Moll. Styes are commonly caused by bacterial infection, or by the blocking of an oil gland at the base of the eyelash. Treatment with antibiotics is indicated if condition leads to preseptic cellulitis and the course ranges from **7 to 10 days.**
Diseases of the Nervous System and Sense Organs	Disorders of the Eye and Adnexa (360 – 379): Disorders of the Lacrimal system	375	375.0	375.00 Dacryoadenitis, unspecified 375.01 Acute dacryoadenitis 375.02 Chronic dacryoadenitis 375.03 Chronic enlargement of lacrimal gland	Dacryoadenitis is inflammation of the lacrimal glands (the tear-producing glands). Also described as a blocked tear duct. Acute dacryoadenitis is most commonly due to viral or bacterial infection. Chronic dacryoadenitis: in most cases, treat the underlying systemic condition. If the enlargement does not subside after **2 weeks**, consider lacrimal gland biopsy
			375.3		Acute dacryocystitis with orbital cellulitis necessitates hospitalization with intravenous (IV) antibiotics. IV empiric antibacterial therapy against penicillin resistant staphylococcus (nafcillin or cloxacillin) should be initiated immediately. (**7 to 10 days**)

Diseases of the Nervous System and Sense Organs	Disorders of the Eye and Adnexa (360 – 379): Disorders of the orbit	376	376.0		Typically, intravenous antibiotic therapy should be continued for **1 to 2 weeks** and then followed by oral antibiotics for an additional **2 to 3 weeks (3-5 weeks in all).**
Diseases of the Nervous System and Sense Organs	Diseases of Ear and Mastoid Process (380 – 389): Disorders of the external ear	380	380.0	Chondritis of pinna – chondritis of auricle/perichondritis of auricle: 380.00 Perichondritis of pinna, unspecified 380.01 Acute perichondritis of pinna 380.02 Chronic perichondritis of pinna 380.03 Chondritis of pinna	Perichondritis is infection of the perichondrium of the pinna in which pus accumulates between the cartilage and the perichondrium. Systemic antibiotics are initiated with an aminoglycoside and semisynthetic penicillin. In mild cases, treatment duration ranges from **10 to 14 days**.
			380.1	Infective otitis externa: 380.10 Infective otitis externa, unspecifie Otitis externa (acute): NOS circumscribed diffuse hemorrhagica infective NOS 380.11 Acute infection of pinna	It also occurs in many other species. Inflammation of the skin of the ear canal is the essence of this disorder. The inflammation can be secondary to dermatitis (eczema) only, with no microbial infection, or it can be caused by active bacterial or fungal infection Effective medications include ear drops containing antibiotics to fight infection, and corticosteroids to reduce itching and inflammation. In painful cases a topical solution of antibiotics including aminoglycosides, polymyxin, quinolones is usually prescribed. Antibiotic ear drops should be dosed in a quantity that allows

					coating of most of the ear canal and used for no more than **4 to 7 days.**
			380.2	Other otitis externa	
Diseases of the Nervous System and Sense Organs	Diseases of Ear and Mastoid Process (380 – 389): Nonsuppurative otitis media and Eustachian tube disorders	381	381.0	Acute nonsuppurative otitis media:	Treatment is with antibiotics and the duration ranges anywhere from **5 to 10 days**.
			381.1	Chronic serous otitis media (complications)	Serous otitis media describes a collection of fluid in the middle ear. This may be acute or chronic. Chronic serous otitis media may result from long-standing eustachian tube blockage or from thickening of the fluid so that it cannot be absorbed or drained down the tube. Chronic serous otitis media can last up to **3 months**.
			381.2	Chronic mucoid otitis media (complications)	
			381.3	Other and unspecified chronic nonsuppurtitive otitis media (complications)	
			381.4	Nonsuppurative otitis media, not specified as acute or chronic	
Diseases of the Nervous System and Sense Organs	Diseases of Ear and Mastoid Process (380 – 389): Suppurative and unspecified otitis media	382	382.0	Acute suppurative otitis media: 382.00 Acute suppurative otitis media without spontaneous rupture of ear drum 382.01 Acute suppurative otitis media with spontaneous rupture of ear drum 382.02 Acute suppurative otitis media in diseases classified elsewhere	Acute otitis media (AOM) is most often purely viral and self-limited, as is its usual accompanying viral URI (upper respiratory infection). If the middle ear, which is normally sterile, becomes contaminated with bacteria, pus and pressure in the middle ear can result, and this is called acute bacterial otitis media. Viral acute otitis media can lead to
			382.1	Chronic tubotympanic suppurative otitis media (complications)	

			382.2	Chronic atticoantral suppurative otitis media (complications)	bacterial otitis media in a very short time The first line antibiotic treatment, if warranted, is amoxicillin. If the bacteria is resistant, then amoxicillin-clavulanate or another penicillin derivative plus beta lactamase inhibitor is second line. **Five days** of treatment has been found to be as effective as **10 days** in otherwise healthy children.
			382.3	Unspecified chronic suppurative otitis media (complications)	
			382.4	Unspecified suppurative otitis media	
			382.9	Unspecified otitis media	
Diseases of the Nervous System and Sense Organs	Diseases of Ear and Mastoid Process (380 – 389): Mastoiditis and related conditions	383	383.0	Acute mastoiditis 383.02 Acute mastoiditis without complications 383.01 Subperiosteal abscess of mastoid 383.02 Acute mastoiditis with other complications Gradenigo's syndrome	Acute mastoiditis, also known as classic mastoiditis, is a rare complication of acute otitis media (AOM). Intravenous antibiotics are indicated for **24-48 hours**. Chronic mastoiditis requires urgent surgical intervention involving drainage and evacuation of the infection and removal of the mastoid process (mastoidectomy). Surgery is followed by a prolonged course of antibiotic therapy, **4 to 6 weeks** or longer. Petrostitis: petrous apicitis is a form of osteitis and should be treated as osteitis. Antibiotic treatment ranges from **3 to 5 weeks**.
			383.1	Chronic mastoiditis (complication)	
			383.2	Petrositis (complication) 383.20 Petrositis, unspecified 383.21 Acute petrositis 383.22 Chronic petrositis	
			383.9	Unspecified mastoiditis	
Diseases of the Nervous System and Sense Organs	Diseases of Ear and Mastoid Process (380 – 389): Other disorders of the tympanic membrane	384	384.0	Acute myringitis without mention of otitis media 384.00 Acute myringitis, unspecified Acute tympanitis NOS 384.01 Bullous myringitis Myringitis bullosa hemorrhagica 384.09 Other	Infectious myringitis is an infection of the eardrum that usually follows a bacterial or viral ear infection. Antibiotic treatment duration is typically **10 to 12 days**. Myringitis becomes chronic when symptoms do not resolve for over **3 months**. Tympanic membrane perforations: Systemic antibiotics are occasionally used when controlling otorrhea from a TMP.
			384.1	Chronic myringitis without mention of otitis media	

				(complications)	Antibiotics directed at typical respiratory flora suffice in most cases. If the ear becomes infected, amoxicillin 500 mg po q 8 h is given for **7 days**.
			384.2	Perforation of tympanic membrane	
			384.3	Perforation of tympanic membrane, unspecified	
Diseases of the Circulatory System (390-459)	Other forms of heart disease (420-429)	420-421	420	Acute pericarditis (complications)	Antibiotics: Initial therapy should include a combination of penicillin antibiotics and third-generation cephalosporins. Duration of therapy is empiric but generally continues for **3 to 4 weeks** with an antibiotic specific to the organism isolated.
			421	Acute and subacute endocarditis (complications)	Penicillin-susceptible streptococcal endocarditis (PSSE) on native cardiac valves is treated with penicillin G for **4 weeks** or penicillin or ceftriaxone combined with gentamicin for **2 weeks**. Penicillin-resistant streptococcal endocarditis (PRSE) on native cardiac valves is treated with penicillin, ampicillin, or ceftriaxone for **4 weeks** combined with gentamicin for the first 2 weeks.
Diseases of the Respiratory System (460-519)	Acute Respiratory Infections	460-466	460	Acute nasopharyngitis (common cold)	
			461	Acute sinusitis: 461.0 – Maxillary 461.1 – Frontal 461.2 – Ethmoidal 461.3 – Spenoidal 461.8 – Other acute sinusitis 461.9 - Acute sinusitis, unspecified	The vast majority of cases of sinusitis are caused by viruses and will therefore resolve without antibiotics. However, if symptoms do not resolve within 7 days, amoxicillin is a reasonable antibiotic to use first for treatment——with amoxicillin/clavulanate being indicated when the patient's symptoms do not improve on amoxicillin alone. Fluoroquinolones and some of the newer macrolide antibiotics such as clarithromycin and doxycycline are used

			in patients who are allergic to penicillins Tretament duration usually lasts from **10 to 12 days.**
	462	Acute pharyngitis	Antibiotics are useful if a group A streptococcus is the cause of the sore throat. Outpatient antibacterial therapy can range from **5 to 10 days**.
	463	Acute tonsillitis	If the tonsillitis is caused by bacteria, then antibiotics are prescribed, with penicillin being most commonly used. Outpatient antibacterial therapy generally lasts for approximately **10 to 14 days.**
	464	Acute laryngitis and tracheitis: 464.0 – Acute laryngitis 464.1 – Acute tracheitis 464.2 – Acute laryngotracheitis 464.3 – Acute epiglottitis 464.4 – Croup 464.5 – Supraglottitis, unspecified	In minor bacterial cases, it can be simply treated with a course of antibiotics. Laryngitis is categorized as acute if it lasts less than a **few days**. Bacterial tracheitis is a bacterial infection of the trachea and is capable of producing airway obstruction. Intravenous antibiotics are administered upon hospital admission for 48-72 hrs. Patients were transition to oral antibiotic therapy for **10 to 14 days** after discharge.
	465	Acute upper respiratory infections of multiple or unspecified sites 465.0 – Acute laryngopharyngitis 465.8 – Other multiple sites 465.9 – Unspecified sites	
	466	Acute bronchitis and bronchiolitis: 466.0 – Acute bronchitis 466.1 – Acute bronchiolitis	Only about 5-10% of bronchitis cases are caused by a bacterial infection. Most cases of bronchitis are caused by a viral infection and are "self-limited" and resolve themselves in a few weeks. Acute

					bronchitis should not be treated with antibiotics unless microscopic examination of the sputum reveals large numbers of bacteria. Treatment can range from **5 to 14 days**.
Diseases of the Respiratory System	Other Diseases of the Upper Respiratory Tract (470-478)**	472	472.1	Chronic pharyngitis* (complications)	Patients can develop this condition as a result of recurrent acute pharyngitis, where infections come and go within the span of about a week. Immediate treatment can include anti-inflammatory medications to reduce the swelling in the throat and make the patient more comfortable, along with antibiotic or antiviral medications to kill infectious organisms in the throat. Antibacterial treatment is the same as its acute form.
			472.2	Chronic nasopharyngitis* (complications)	Same as above
		473	473	Chronic sinusitis* (complications)	if symptoms do not resolve within 10 days, amoxicillin is a reasonable antibiotic to use first for treatment with amoxicillin /clavulanate being indicated when the patient's symptoms do not improve on amoxicillin alone
		474	474.0	Chronic tonsillitis and adenoiditis*(complications)	Tonsillitis that is caused by a bacterial infection is usually treated with a **10 to 14-day** course of antibiotics, given either as a one-time injection or orally. Penicillin is the drug of choice for tonsillitis. Chronic tonsillitis is a recurrent form of acute tonsillitis. Adenoiditis may be treated with antibiotics if symptoms do not improve after **10 to 12 days**. Again, adenoiditis is a recurrent form of acute adenoiditis.

	475	475	Peritonsillar abscess (complications)	Peritonsillar abscess is a complication of tonsillitis. It is most often caused by a type of bacteria called *group A beta-hemolytic streptococcus*. Antibiotic therapy should begin after cultures are obtained from the abscess. The use of high-dose intravenous penicillin remains a good choice for the empiric treatment of PTA. The patient may be prescribed oral antibiotics once oral intake is tolerated; length of treatment should **be 7 to 10 days after IV.**
	476	476	Chronic laryngitis and laryngotracheitis* (complications)	*S aureus* is a frequent causative organism in cases of chronic bacterial laryngitis. Antimicrobial therapy should cover gram-positive and gram-negative pathogens. It can last up to **3 months.**
	478	478.1	Other diseases of the nasal cavity and sinus (complications) 478.19 Other disease of nasal cavity and sinuses Includes **abscess** of nose (septum)	Abscesses occur as a result of a complication from prior antimicrobial therapy for infection. Symptoms should resolve after a **2-week** course of oral antibiotic therapy.
		478.2	Other diseases of the pharynx, not elsewhere classified (complications) 478.21 Cellulitis of pharynx or nasopharynx 478.22 Parapharyngeal abscess 478.23 Retropharyngeal abscess	Parapharyngeal abscess: Several days of parenteral culture-determined antibiotics are required after drainage, followed by **10 to 14 days** of oral antibiotics. Retropharyngeal abscess: Antibiotics, such as a broad-spectrum cephalosporin (eg, ceftriaxone 50 to 75 mg/kg IV once/day. However, most patients also require drainage through an incision in the posterior pharyngeal wall.
		478.5	Other diseases of the vocal cords (complications) Abscess/Cellulitis of vocal cords	

			478.7	Other diseases of larynx, not elsewhere classified (complications) 478.71 Cellulitis and perichondritis of larynx 478.79 Other: includes abscess of larynx	
			478.9	Other and unspecified diseases of upper respiratory tract: includes abscess of trachea (complications)	
Diseases of the Respiratory System	Pneumonia & Influenza (480-487)	481-486	481	Pneumococcal pneumonia (streptococcus pneumoniae pneumonia)	In North America, where the "atypical" forms of community-acquired pneumonia are becoming more common, clarithromycin, azithromycin, or fluoroquinolones as single therapy, have displaced the amoxicillin as first-line therapy. Bacterial pneumonia is generally treated with antibiotics and outpatient therapy can range anywhere from **7 to 14 days**. Bronchopneumonia: Upon diagnosis, most people will be treated at home with antibiotics. With appropriate treatment, most people recover fully within a **couple weeks.**
			482	Other bacterial pneumonia:	
			483	Pneumonia due to other organism: 483.0 Mycoplasma pneumoniae 483.1 Chlamydia 483.8 Other specified organism	
			484	Pneumonia in infectious diseases classified elsewhere	
			485	Bronchopneumonia	
			486	Pneumonia, organism unspecified	
Diseases of the Respiratory System	Other diseases of the respiratory system (510-519)	513	513	Abscess of lung (complications)* 513.0 Abscess of lung 513.1 Abscess of mediastinum	Although the duration of therapy is not well established, most clinicians generally prescribe antibiotic therapy for **4 to 6 weeks**.
		519	519.2	Mediastinitis (complications)*	Appropriate, well-directed antibiotic therapy is crucial to successful treatment of mediastinitis. One study suggests that **4 to 6 weeks** of therapy is adequate for most patients.

Diseases of the Digestive System (520-579)	Diseases of oral cavity, salivary glands and jaws (520-529)	522	522.0	Pulpitis Includes abscess	Dental abscess: when drainage cannot be achieved or the patient shows signs of systemic involvement, antibiotic therapy is indicated. Oral antibiotic treatment generally lasts approximately **10 days**. Salivary gland abscess: Patients are most often treated on an outpatient basis, with the administration of a single dose of parenteral antibiotics in an emergency department, followed by oral antibiotics for a period of **7 to 10 days.** Glossitis: Antibiotics may be prescribed if the cause of glossitis is an infection. The signs of infection should resolve in **7 days**
			522.5	Periapical abscess without sinus	
			522.7	Periapical abscess with sinus	
		527	527.3	Abscess of salivary glands	
		528	528.3	Cellulitis and abscess of mouth	
			528.5	Diseases of lips Includes abscess of lips	
		529	529.0	Glossitis Includes abscess	
Diseases of the Digestive System (520-579)	Diseases of esophagus, stomach and duodenum (530-538)	530-535	530.2	Esophageal ulcer (acute)	*Helicobacter pylori* colonizes the stomach of more than half of the world's population, and the infection continues to play a key role in the pathogenesis of a number of gastroduodenal diseases. Colonization of the gastric mucosa with *Helicobacter pylori* results in the development of chronic gastritis in infected individuals. Several regimens are used to treat *H. pylori* infection. Most use a combination of two antibiotics and a proton pump inhibitor. Regimens aregiven for a total of **2 weeks**.
			531.0-.3	Gastric ulcer (acute)	
			532.0-.3	Duodenal ulcer (acute)	
			533.0-.3	Peptic ulcer, site unspecified (acute)	
			534.0-.3	Gastrojejunal ulcer (acute)	
			535.5, 535.6	Gastritis and duodenitis 535.5 – Unspecified gastritis and duodenitis 535.6 – Duodenitis	
Diseases of the Digestive System (520-579)	Other diseases of intestines and peritoneum (560-569)	566	566	Abscess of anal and rectal regions	Peritonitis: Empiric therapy with a third-generation cephalosporin must begin promptly and can subsequently be narrowed according to the culture results. Traditionally, a course of **10 days** is recommended, although studies have
		567	567.0	Peritonitis in infectious diseases classified elsewhere	
			567.1	Pneumococcal peritonitis	
			567.2	Other suppurative peritonitis	

			567.3	Retroperitoneal infections	suggested that **5 days** of therapy may be sufficient in most cases.
			567.9	Unspecified peritonitis	
		569	569.5	Intestinal abscess (complication)	
Diseases of the Genitourinary System (580-629)	Nephritis. Nephoitic syndrome, and nephrosis (580-589)	580	580	Acute glomerulonephritis	Antibiotic therapy is used to treat the infection that resulted in acute glomerulonephritis. Treatment is supportive, and the disease generally resolves in **2 to 4 weeks**.
Diseases of the Genitourinary System (580-629)	Other Diseases of Urinary System (590-599): Infections of kidney	590	590.0	Chronic pyelonephritis *(complications) (chronic pyelitis, chronic pyonephrosis)	As practically all cases of pyelonephritis are due to bacterial infections, antibiotics are the mainstay of treatment. Mild cases may be treated with oral therapy, but generally intravenous antibiotics are required for the initial stages of treatment. The acute form duration of treatment is **10 to 14 days**, while chronic form results from recurrent infections and may last a long time. Abscesses usually occur as a complication of UTIs. Appropriate oral antibiotics are given throughout the drainage/sclerosant period and for **1 to 3 weeks** after the drainage tube is withdrawn.
			590.1	Acute pyelonephritis	
			590.2	Renal and perinephric abscess (complications)	
			590.8	Other pyelonephritis or pyonephrosis, not specified as acute or chronic	
			590.9	Infection of the kidney, unspecified	
Diseases of the Genitourinary System	Other Diseases of Urinary System (590-599): Cystitis	595	595.0	Acute cystitis	Acute cystitis is an infection of the bladder that occurs suddenly and follows a short, but severe course. Cystitis should be promptly treated. Antibiotics are used to fight the bacterial infection. For a simple bladder infection, you will take antibiotics for 3 days (women) or **7 to 14 days** (men). For a bladder infection with complications such as pregnancy or

					diabetes, OR a mild kidney infection, you will usually take antibiotics for 7 - 14 days.
Diseases of the Genitourinary System	Other Diseases of Urinary System (590-599): Urethritis, not sexually transmitted	597	597.0	Urethral abscess (complications)	Urethral abscesses typically occur due to a complication of previous UTIs.
			597.8	Other urethritis	A variety of drugs may be prescribed based on the cause of the patient's urethritis. Antibiotic therapy duration can range up to **7 days**.
Diseases of the Genitourinary System	Other Diseases of Urinary System (590-599): Other disorders of the urethra and urinary tract	599	599.0	Urinary tract infection, unspecified	Oral antibiotics such as trimethoprim, cephalosporins, nitrofurantoin, or a fluoroquinolone such as ciprofloxacin substantially shorten the time to recovery. About 50% of people will recover without treatment within a few days or weeks. Antibacterial treatment for UTIs can last anywhere from **3 to 14 days**.
Diseases of the Genitourinary System	Diseases of the Male Genital Organs (600-608): Inflammatory diseases of the prostate	601	601.0	Acute prostatitis (complications)	Antibiotics are the first line of treatment in acute prostatitis. Antibiotics usually resolve acute prostatitis infections in a very short time. Appropriate antibiotics should be used, based on the microbe causing the infection. Ciprofloxacin, co-trimoxazole and tetracyclines such as doxycycline penetrate the prostate capsule well. Treatment is continued orally for **30 days**.
			601.1	Chronic prostatitis (complications)*	Treatment requires prolonged courses (**4 to 8 weeks**) of antibiotics that penetrate the prostate well.

			601.2	Abscess of the prostate (complications)	Abscess typically occurs due to antibiotic failure of initial acute prostatitis.
			601.3	Prostatocystitis	
			601.4	Prostatitis in diseases classified elsewhere	
			601.8	Other specified Inflammatory diseases classified elsewhere: Prostatitis: cavitary diverticular granulomato us	
			601.9	Prostatitis unspecified	
Diseases of the Genitourinary System	Diseases of the Male Genital Organs (600-608)	604	604	Orchitis and epididymitis	Orchitis is an inflammation of testicle tissue and epididymitis is a medical condition in which there is inflammation of the epididymis. Treatment includes antibiotics for **7 days.**
		607	607.2	Other inflammatory disorders of the penis: Abscess of corpus cavernosum or penis Boil of corpus cavernosum or penis Carbuncle of corpus cavernosum or penis Cellulitis of corpus cavernosum or penis Cavernitis (penis) Use additional code to identify organism	
		608	608	Seminal vesiculitis	Appropriate use of antibiotics, treatment of the symptoms of acute Seminal should disappear, then continue medication **1 to 2 weeks**.
Diseases of the Genitourinary System	Disorders of the Breast (610-612)	611	611.1	Inflammatory disease of breast: Includes abscess	Breast abscesses are usually treated with a **7 day** course of antibiotics.

Diseases of the Genitourinary System	Inflammatory disease of female pelvic organs (614-616)	614	614.0	Acute salpingitis and oophoritis	Salpingitis is most commonly treated with antibiotics. Antibacterial treatment up to **14 days** can cover gonorrhea and chlamydia infection.
			614.1	Chronic salpingitis and oophoritis (complication)*	
			614.2	Salpingitis and oophoritis not specified as acute, subacute or chronic	
			614.3	Acute parametritis and pelvic cellulitis	Parenteral administration is recommended for at least the initial **4 days** of therapy, but orally administered drugs may be evaluated for completion of longer courses.
			614.4	Chronic or unspecified parametritis and pelvic cellulitis (complication)*	
			614.5	Acute or unspecified pelvic peritonitis	Acute peritonitis: empiric therapy with a third-generation cephalosporin must begin promptly and can subsequently be narrowed according to the culture results. Traditionally, a course of **10 days** is recommended
			614.7	Other chronic pelvic peritonitis, female (complication)*	
			614.9	Unspecified inflammatory disease of female pelvic organs and tissues: pelvic infection or inflammation	
		615	615.9	Unspecified inflammatory disease of uterus Endometritis Metritis Myometritis Perimetritis Pyometra Uterine abscess	Antibiotic therapy is curative in most cases (depending on underlying etiology), with fairly rapid alleviation of symptoms after only **2 to 3 days**.
		616	616.0	Cervicitis and endocervicitis	Oral antibiotics effectively cure gonorrhea, chlamydia, and *T vaginalis* infections. Outpatient antibacterial treatment duration ranges from **7 to 10 days**.

			616.1	Vaginitis and vulvovaginitis	Recommended regimens for *T vaginalis* infection include the following: Metronidazole 2 g orally in a single dose, tinidazole 2 g orally in a single dose or ann alternative regimen is metronidazole 500 mg orally twice a day for **7 days.**
			616.3	Abscess of Bartholin's gland	A Bartholin's abscess forms when a small opening (duct) from the gland gets blocked. Antibiotics may be prescribed, but they are not usually needed if the abscess is drained properly. Outpatient therapy can last up to **7 days** post drainage.
			616.4	Other abscess of vulva	These abscesses most commonly originate as simple infections that develop in the vulvar skin or subcutaneous tissues superficial to the fascia.
Diseases of the Skin and Subcutaneous Tissue (680-709)	Infections of the skin and subcutaneous tissue	680-686	680	Carbuncle and furuncle	A carbuncle can simply be defined as multiple furuncles grouped together. A carbuncle usually involves the deeper layers of the skin - the subcutaneous fat. Furuncle is an infection of the pilosebaceous unit, therefore is more extensive than a folliculitis because the infection also involves the sebaceous gland. More extensive furuncles and all carbuncles need to be treated with antibiotics such as dicloxacillin or cephalexin. Treatment ranges from **10 to 14 days**.

	681	Cellulitis and abscess of finger and toe	Cellulitis is a diffuse inflammation of connective tissue with severe inflammation of dermal and subcutaneous layers of the skin. Flucloxacillin or Dicloxacillin monotherapy (to cover staphylococcal infection) is often sufficient in mild cellulitis, but in more moderate cases, or where streptococcal infection is suspected, then this course is usually combined with oral phenoxymethylpenicillin or intravenous benzylpenicillin, or ampicillin/amoxicillin. Outpatient therapy generally ranges from **10 to 14 days.**
	682	Other cellulitis and abscess: 682.0 – Face 682.1 – Neck 682.2 – Trunk (abdominal/chest wall) 682.3 – Upper arm and forearm 682.4 – Hand, except fingers and thumb 682.5 – Buttock 682.6 – Leg, except foot 682.7 – Foot, except toes 682.8 – Other specified sites 682.9 – Unspecified site	
	683	Acute lymphadenitis: Abscess (acute) lymph gland or node, except mesenteric Adenitis, acute lymph gland or node, except mesenteric Lymphadenitis, acute lymph gland or node, except mesenteric Use additional code to identify organism such as Staphylococcus (041.1)	The acute lymphadenitis (inflamation of lymph nodes) is characterized by bacterial invasion from injured skin or mucosal or from other pahological site. Treatment with antimicrobial therapy that usual lasts **10 days.**
	684	Impetigo	Impetigo is a highly contagious bacterial skin infection most common among pre-school children. Mild cases may be treated with bactericidal ointment, such as fusidic acid, mupirocin, chloramphenicol or neosporin, which in some countries may be available over-the-counter. More severe cases require oral antibiotics, such as dicloxacillin, flucloxacillin or erythromycin. A **7 day** course of

					antibiotics is usually standard
			685.0	Pilonidal cyst with abscess	
			686	Other local infections of skin and subcutaneous tissue: 686.8 – Other specified local infections of skin and subcutaneous tissue 686.9 – Unspecified local infection of skin and subcutaneous tissue	
Diseases of the Musculoskeletal System and Connective Tissue (710-739)	Rheumatism, excluding the back (725-729.9)	728	728.0	Infective myositis (complications)	Infectious myositis is an acute, subacute, or chronic infection of skeletal muscle. Antibiotics initially are given intravenously until clinical improvement is noted, followed by oral antibiotics for a total course of **approximately 1 month.**
			728.8	728.86 – Necroizing Fasciitis (complications)	**Necrotizing fasciitis** (**NF**), commonly known as **flesh-eating disease** or **Flesh-eating bacteria syndrome**,[1] is a rare infection of the deeper layers of skin and subcutaneous tissues, easily spreading across the fascial plane within the subcutaneous tissue. It typically requires hospitalization and treatment with IV antibiotics.
Diseases of the Musculoskeletal System and Connective Tissue (710-739)	Osteopathies, chondropathies and acquired musculoskeletal deformities (730-739)**	730	730.0	Acute osteomyelitis (complications)	Osteomyelitis is an infective process that encompasses all of the bone components, including the bone marrow. When it is chronic, it can lead to bone sclerosis and deformity. Chronic osteomyelitis may be due to the presence of intracellular bacteria (inside bone cells). Osteomyelitis often requires prolonged antibiotic
			730.1	Chronic osteomyelitis (complications)	
			730.2	Unspecified osteomyelitis (complications)	

					therapy, with a course lasting a matter of weeks or months. Treatment is required for at least **4 to 6 weeks**.
			730.3	Periostitis without mention of osteomyelitis (complications)	Acute periostitis is due to infection and is characterized by diffuse formation of pus, severe pain, constitutional symptoms, and usually results in necrosis.
			730.8	Other infections involving bone in diseases classified elsewhere (complications)	
			730.9	Unspecified infection of bone (complications)	
Symptoms, Signs and Ill-Defined Conditions (780-799)	Symptoms (780-789.9)**	785	785.4	Gangrene (complications)	Antibiotics and surgery are the primary treatments and have been proven very effective. Hospitalization is necessary for treatment.
			785.5	Shock without mention of trauma (complications) 785.52 – Septic shock	
Symptoms, Signs and Ill-Defined Conditions (780-799)	Non-specific abnormal findings (790-796.9)**	790	790.7	Bacteraemia, unspecified (complications)	Bacteria can enter the bloodstream as a severe complication of infections, during surgery, or due to catheters and other foreign bodies entering the arteries or veins.
Injury and Poisoning (800-999)	Complications of Surgical and Medical Care, NEC (996-999)	998	998.0	Postoperative shock (complications) Includes: Shock (septic)	
			998.5	Postoperative infection (complications)	
Injury and Poisoning (800-999)	Complications of Surgical and Medical Care, NEC (996-999)	999	999.3	Other infection	

Infections having more than 21 days of required antibiotic therapy or known to be a chronic or complication of infection (shown in red) were only included during the outcome assessment period when identifying cases of ATF. For study population selection purposes, only patients with acute infections were included. *Treatment for each condition was compiled and verified through www.medscape.com

Table A2. 3 – Charlson Comorbidity Index Conditions[250]

COMORBID CONDITION	ICD-9 CODES	DESCRIPTION	CCI SCORE
1. **Myocardial infarction**	410-410.9 412	Acute myocardial infarction Old myocardial infarction	1
2. **Congestive heart failure**	428-428.9	Heart failure	1
3. **Peripheral vascular disease**	443.9 441.0-441.9 785.4 V43.4	Peripheral vascular disease, including intermittent claudication Aortic aneurysm Gangrene Blood vessel replaced by prosthesis	1
4. **Cerebrovascular disease**	430-438	Cerebrovascular disease	1
5. **Dementia**	290-290.9	Senile and presenile dementias	1
6. **Chronic pulmonary disease**	490-496 500-505 506.4	Chronic pulmonary obstructive disease Pneumoconioses Chronic respiratory conditions due to fumes and vapors	1
7. **Rheumatologic disease**	710.0 710.1 710.4 714.0-714.2 714.81 725	Systemic lupus erythematosus Systemic sclerosis Polymyositis Adult rheumatoid arthritis Rheumatoid lung Polymyalgia rheumatica	1
8. **Peptic ulcer disease**	531-534.9 531.4-531.7 532.4-532.7 533.4-533.7 534.4-534.7	Gastric, duodenal, and gastrojejunal ulcers Chronic forms of peptic ulcer disease	1

9. **Mild liver disease**	571.2 571.5 571.6 571.4-571.49	Alcoholic cirrhosis Cirrhosis without mention of alcohol Biliary cirrhosis Chronic hepatitis	1
10. **Diabetes**	250-250.3 250.7	Diabetes with or without acute metabolic disturbances Diabetes with peripheral circulatory disorders	1
11. **Diabetes with chronic complications**	250.4-250.6	Diabetes with renal, ophthalmic, or neurological manifestations	2
12. **Hemiplegia or paraplegia**	344.1 342-342.9	Paraplegia Hemiplegia	2
13. **Renal disease**	582-582.9 583-583.7 585 586 588-588.9	Chronic glomerulonephritis Nephritis and nephropathy Chronic renal failure Renal failure, unspecified Disorders resulting from impaired renal function	2
14. **Any malignancy, including lymphoma and leukemia**	140-172.9 174-195.8 200-208.9	Malignant neoplasms Malignant neoplasms Leukemia and lymphoma	2
15. **Moderate or severe liver disease**	572.2-572.8 456.0-456.21	Hepatic coma, portal hypertension, other sequelae of chronic liver disease Esophageal varices	3
16. **Metastatic solid tumor**	196-199.1	Secondary malignant neoplasm of lymph nodes and other organs	6
17. **AIDS**	042-044.9	HIV infection with related specified conditions	6

Table A2.4 – SSTIs Commonly Linked to Community-Acquired MRSA

TYPE OF SSTI	ICD-9 CODES	REFERENCE
Cellulitis	528.3, 614.3, 681, 682	Napolitano, L. Severe Soft Tissue Infections. *Infect Dis Clin N Am* 23 (2009) 571–59.
Necrotizing Fasciitis	728.86	
Pyomyositis	728.0	
Gas Gangrene	040.0	
Impetigo	035	
Abscess	254.1, 478.1, 478.2, 522.0, 522.5, 522.7, 527.3, 528.3, 528.5, 529.0, 566, 611.1, 616.3, 616.4, 685.0	

Table A2.5 – Definition of Socioeconomic Status

SES CATEGORY	HEALTH SURVEY CODE	INCOME RANGE FOR NO. OF PERSONS/HOUSEHOLD
Low Income	SUFRER92/98, Codes 1 & 2	< 15 000 for 1-2 persons <20 000 for 3-4 persons <30 000 for 5+ persons
Middle Income	SUFRER92/98, Codes 3 & 4	15 000 – 59 999 for 1-2 persons 20 000 – 79 999 for 3-4 persons 30 000 – 79 999 for 5+ persons
High Income	SUFRER92/98, Code 5	60 000+ for 1-2 persons 80 000+ for 3+ persons

A2.1 Defining the Study Population

1. Restrict age:
    - Drop 80+ years of age at the time of the health survey
    - Record the number of persons dropped: **220** **N =** 17 794

2. Restrict weight categories:
    - Remove all those who have height and/or weight measurements missing at baseline
        - o Remove women who are pregnant at the time of the health survey (already taken into account since BMIs are not computed for this subset of participants).
        - o Record the number of persons missing BMI: **480** **N =** 17 314
    - Apply a BMI correction for self-reported weight values:
        - o Male: -1.08 + (1.08 x self-reported BMI)
        - o Female: -0.12 + (1.05 x self-reported BMI)
    - Use the corrected BMI values to include the normal (18.5-24.9), overweight (25-29.9) and obese (≥30) weight categories in the cohort.
        - o Drop and record the number of underweight individuals: **281** **N =** 17 033

3. Restrict patients to only those receiving at **least one oral antibiotic** OR **hospitalization for an acute infection** during the course of follow up (from the date of the survey to 2005):
    - Include only those who received capsules/tablets/oral suspensions or those who have had a hospital admission for an acute infection (either primary or secondary infectious causes) as defined by the ICD-9 codes below during the course of follow-up.
        - o Antibiotic AHFS class codes of interest at T_0 used: 081202, 081206, 081207, 081208, 081212, 081216, 081218, 081220, 081224, 081228, 082200, 082400, 083600, 520404, 520408, 520412, 520492, 084000, 089200, 840404, 840416, 840492
        - o Antibiotic outpatient oral forms used at T_0: 116, 203, 406, 435, 464, 638, 2842, 4234, 4959, 4988, 5481, 5561, 5568
        - o ICD-9 codes corresponding to possible infections at T_0: 002, 003.0, 003.8, 003.9, 004, 006, 007.0, 007.3, 007.5, 008.0-008.5, 009.0-009.3,021, 026, 027.1, 032-037, 040.1, 040.3, 040.8, 041, 073, 077.0, 080-083, 087, 090-099, 100-104, 245.0, 254.1, 320, 360.0, 370.0-370.5, 370.8, 370.9, 372.0, 372.2, 373.1, 375.0, 375.3, 380.0-380.2, 381.0, 381.4, 382.0, 382.4, 382.9, 383.0, 383.9, 384.0, 384.2, 384.3, 460-466, 478.1, 478.2, 481-483, 485, 486, 522.0, 522.5, 522.7, 527.3, 528.3, 528.5, 529.0, 530.2, 531.0-531.3, 532.0-532.3, 533.0-533.3, 534.0-534.3, 535.5, 535.6, 566, 567.0-567.3, 567.9, 580, 590.1, 590.8, 590.9, 595.0, 597.8, 599.0, 601.3, 601.4, 601.8, 601.9, 604, 607.2, 608, 611.1, 614.0, 614.2, 614.3, 614.5, 614.7, 614.9, 615.9, 616.0, 616.1, 616.3, 616.4, 680-684, 685.0, 686, 999.3.
    - Create T_0 = time at receipt of first oral antibiotic prescription or discharge date of first hospitalization for an acute infection, whichever comes first during the course of follow-up.

- Patients dropped with assigned T_0 in 2006: **286**
- Drop patients who were hospitalized for infection at T_0, but had a total LOS > 30 days: **87**
- Record the number of individuals in each weight category receiving at least one antibiotic script or hospitalization for infection at T_0 in the table below:

WEIGHT CATEGORY	PATIENTS WITH AT LEAST ONE ANTIBIOTIC/HOSPITALIZATION (N, %)	PATIENTS WITH NO ANTIBIOTIC OR HOSPITALIZATION (N, %)	TOTAL (N)
Normal	3 181 (44.4)	3 986 (55.6)	7 167
Overweight	2 964 (44.1)	3 748 (55.8)	6 712
Obese	1 653 (52.4)	1 501 (47.6)	3 154
Total	7 798(45.8)	9 235 (54.2)	17 033

- Create T_1 (cut-off time for outcome assessment) = T_0+30 days, since the outcome assessment period spans from T_0-T_1.
- Record the number of patients in the infection cohort: **N = 7 798**

4. Apply other exclusion criteria relating to health status: exclude those with a diagnosis of TB:
    - Patients who have had a diagnosis of TB (ICD-9 codes 010-018) from the year preceding the date of the health survey to T_0 should be excluded using the health survey, Medical Service Claims database, and MED-ECHO database diagnostic codes.
    - Record the number of patients with TB excluded: **63** **N=** 7 735

5. Apply other exclusion criteria related to follow-up (censoring):
    - Exclude patients who were lost to follow-up or who died as a result of a non-infectious cause between T_0 and T_1: **37**
    - Record the sample size after this step: **N =** 7 698

6. Apply other exclusion criteria relating to drug coverage:
    - Exclude those who are not covered under the drug insurance plan from the period just before the receipt of the first antibiotic (T_0) until 30 days post-receipt (at the assessment of the outcome: T_1)
    - Record the number of people not covered under the provincial drug insurance plan during the outcome assessment period: **905** **N =** 6 793

7. Apply other exclusion criteria in relation to weight shift during the course of follow-up
    - Exclude those patients who had bariatric surgery before receipt of the first antibiotic but after the date of the health survey (from baseline to T_1). If bariatric surgery date < outcome assessment date, then delete.
    - Diagnosis codes for obesity were used in combination with intervention codes to define cases:
        - Obesity ICD-9 codes: 278.0 and 278.8 (V45.86 used for bariatric surgery)
        - CCP codes: 56.2, 56.93 and 56.59 (gastric partitioning for obesity)

- Exclude patients who became pregnant from the date of the survey to T_0 as this would increase the likelihood of weight fluctuations. Pregnancy will be defined as having one of the following codes anywhere from the date of the health survey to 6-months post-T_0:
    - o Delivery in a completely normal case: ICD-9 code 650
    - o Complications in labor and delivery: ICD-9 codes 660 to 669
    - o Outcome of delivery: ICD-9 codes V27.0 to V27.7
    - o Induction, instrumental, cesarean delivery: CCP codes 84.0 to 86.2
    - o Other and unspecified cesarean: CCP codes 86.8 to 86.9
    - o Birth not elsewhere classified or specified: CCP code 87.98
- Record the number patients removed due to weight fluctuation: **250**
  N = 6 543

8. Further age restriction at end of outcome assessment period:
    - Drop patients who were 80+ at T_1: **138** **N =** 6 405

9. Recent antibiotic use 30 days prior to T_0:
    - Exclude patients who have had any antibiotic prescription or hospitalization for an acute or non-acute infection in the 30 days prior to T_0 (for those receiving their 1st hospitalization for infection or antibiotic prescription near the date of the health survey): **32**
        - o For this step, do not restrict the form of the antibiotic to oral forms
            - If a non-orally administered antibiotic was given at T_0 in addition to the oral form, these patients will be kept as ATF may still be assessed: **52**
        - o Use the same ICD-9 infection codes as in step 3 for acute infections
        - o Use the following additional ICD-9 codes for the identification of non-acute/chronic infections requiring more than 30 days of antibiotic therapy at T_0: 003.1, 003.2, 038, 040.0, 324, 372.1, 376.0, 381.1-381.3, 382.1-382.3, 383.1, 383.2, 384.1, 420, 421, 472.1, 472.2, 473, 474.0, 475, 476, 478.1, 478.2, 478.5, 478.7, 478.9, 513, 519.2, 569.5, 590.0, 590.2, 597.0, 601.0-601.2, 614.1, 614.4, 728.0, 730.0-730.3, 730.8, 730.9, 785.4, 785.5, 790.7, 998.0, 998.5
            - If non-acute/chronic infection is identified on the same day as T_0 for an acute infection, we will remove them as we do not know whether the antibiotic prescription is for the acute or non-acute infection, which may require a longer course of antibiotics with respect to the outcome assessment period
    - Record the number of people with recent antibiotic use/hospitalization with a non-acute infectious cause in the 30 days prior to T_0: **194**
    - Total number of patients dropped due to recent antibiotic use: **226**

10. Final Study Population
    - Record the number of patients in the final study population: **N = 6 179**
    - Record the number of morbidly obese patients: **75**

WEIGHT CATEGORY	FREQUENCY (%)
Normal	2 444 (39.6)
Overweight	2 408 (39.0)
Obese	1 327 (21.4)
Total	6 179 (100.0)

A2.2 Creating Exposure, Outcome and Confounding Variables

Outcome: Antibiotic Treatment Failure

Secondary/Additional Antibiotic Prescriptions

1. Restrict outcome assessment to FIRST antibiotic prescriptions dispensed (all forms) or hospital admissions for infections for each participant during the outcome assessment period (i.e. at T_0 +3d – T_1).

2. Create an outcome variable "secondary antibiotic (secab)" for those patients receiving a secondary antibiotic between T_0 + 3d and T_1 (30 days after initial prescription).
    - Secondary antibiotic prescriptions are defined as any additional antibiotic between T_0 +3d and T_1 using the AHF drug classes without restricting to the orally-administered drug form (i.e. can be IV, parenteral, IM etc.)
    - Secondary antibiotic prescriptions need not be identified in combination with corresponding infection ICD-9 codes.

3. If secab=1, then ATF=yes.

4. Record the number of patients having a secondary antibiotic prescription as an ATF event: **807**

Hospitalizations

5. Create an outcome variable for patients "hospitalized for infection (hosinf)" (includes death due to infection: 1) between T_0 and T_1. For the group of patients with T_0 corresponding to a hospitalization for infection, use T_0 (discharge date) as the beginning of the outcome assessment period. For patients hospitalized during the outcome assessment period (i.e. T_0-T_1), determine if the primary or secondary cause of hospital admission was infectious using the ICD-9 diagnostic codes of interest (see below). For patients with a T_0 corresponding to an antibiotic, use T_0 + 3d as the beginning of the outcome assessment period in order to determine if these patients had a hospitalization as an ATF event.
    - Infection ICD-9 codes of interest are: 002, 003.0-003.2, 003.8, 003.9, 004, 006, 007.0, 007.3, 007.5, 008.0-008.5, 009.0-009.3,021, 026, 027.1, 032-038, 040.0, 040.1, 040.3, 040.8, 041, 073, 077.0, 080-083, 087, 090-099, 100-104, 245.0, 254.1, 320, 324, 360.0, 370.0-370.5, 370.8, 370.9, 372.0-372.2, 373.1, 375.0, 375.3, 376.0, 380.0-380.2, 381.0-381.4, 382.0-382.4, 382.9, 383.0-383.2, 383.9, 384.0-384.3, 420, 421, 460-466, 472.1, 472.2, 473, 474.0, 475, 476, 478.1, 478.2, 478.5, 478.7, 478.9, 481-483, 485, 486, 513, 519.2, 522.0, 522.5, 522.7, 527.3, 528.3, 528.5, 529.0, 530.2, 531.0-531.3, 532.0-532.3, 533.0-533.3, 534.0-534.3, 535.5, 535.6, 566, 567.0-567.3, 567.9, 569.5, 580, 590.0-590.2, 590.8, 590.9, 595.0, 597.0, 597.8, 599.0, 601.0-601.4, 601.8, 601.9, 604, 607.2, 608, 611.1, 614.0-614.5, 614.7, 614.9, 615.9, 616.0, 616.1, 616.3, 616.4, 680-684, 685.0, 686, 728.0, 728.8, 730.0-730.3, 730.8, 730.9, 785.4, 785.5, 790.7, 998.0, 998.5, 999.3.

- Additional ICD-9 codes added to this list from the study population list are: 003.1, 003.2, 038, 040.0, 324, 372.1, 376.0, 381.1-381.3, 382.1-382.3, 383.1, 383.2, 384.1, 420, 421, 472.1, 472.2, 473, 474.0, 475, 476, 478.1, 478.2, 478.5, 478.7, 478.9, 513, 519.2, 569.5, 590.0, 590.2, 597.0, 601.0-601.2, 614.1, 614.4, 728.0, 728.8, 730.0-730.3, 730.8, 730.9, 785.4, 785.5, 790.7, 998.0, 998.5.
- If hospital admission was due to an infectious cause, then "hosinf"=1.

- Perform a proc means to determine the length of stay for patients hospitalized at T_1:

WEIGHT CATEGORY	LOS ($\bar{x}$, SD)
Normal	9.8 (10.3)
Overweight	11.2 (16.6)
Obese	6.6 (4.7)

6. If hosinf=1, then ATF=yes

7. Record the number of patients having a hospital admission for infection as an ATF event: **40**

8. Record the total number of UNIQUE patients in the ATF group: $\mathbf{N_{ATF}}$ = **828**

ATF	NORMAL WEIGHT	OVERWEIGHT	OBESE	TOTAL
NO	2 143	2 088	1 120	5 351
YES	301	320	207	828
TOTAL	2 444	2 408	1327	6 179

Confounders and Covariates

1. Sociodemographic Variables:
   - Gender: M/F
   - Age at the time of the outcome assessment (T_1): continuous variable
   - Socioeconomic status: low income, middle income, high income
     - o Low income: variable name SUFRER92/98, codes 1 & 2
     - o Middle income: variable name SUFRER92/98, codes 3 & 4
     - o High Income: variable name SUFRER92/98, code 5

2. Lifestyle Risk Factors:
   - Smoking (current-ever smokers) (yes/no) at the time of the health survey
     - o Non-smokers: TABAC=1 (1992 & 1998 survey code)
     - o Current-ever smokers: TABAC=2-4 (1992 & 1998 survey code)
   - Drinkers (yes/no) at the time of health survey
     - o Non-drinkers: TypeBUV= 1 & 2 (1992 & 1998 survey codes)
       - Defined as those who are abstinent or those who have not had an alcoholic beverage within the year preceding the date of the health survey
     - o Drinkers: TypeBUV=3 (1992 & 1998 survey codes)
       - Non-heavy drinkers: ALCOOL92=0-3, ALCOOL98=0-3

- Heavy drinkers: ALCOOL 92=4, ALCOOL98=4
- Drinkers defined as those who have had at least 1 alcoholic beverage within the week preceding the date of the health survey
- Heavy drinkers defined as ≥29 alcoholic beverages consumed in the week preceding the date of the survey.

3. Comorbidity:
    - Create the CCI using the diagnoses from the Medical Service Claims and MED-ECHO databases ranging from the year preceding the date of the survey to T_0 (receipt of the first antibiotic or hospitalization for infection).
    - The health problems section of the health survey will also be used to create the CCI.

4. Inappropriate Antibiotic Use
    - Create the variable flu season ("flu") as a proxy measure for inappropriate antibiotic use; this confounding variable will only be used for the subgroup of patients with oral antibiotic prescriptions corresponding to their T_0.
        - Flu season = 1 if October-March is the date of receipt for antibiotic prescriptions (T_0)
        - Flu season = 0 if April-September is the date of receipt for antibiotic prescriptions (T_0)
            - ATF rates should not depend on patients receiving antibiotics in either Q1 or Q4 since Q1 (January-March) and Q4 (October-December) are flu season.

5. Previous History of Antibiotic Use:
    - If patients have a history of previous antibiotic use or hospitalization for infection before T_0 and in the year prior to the health survey, then abhis=1.
    - Record the number of people with previous history of antibiotic use: **1 767**

6. Type of Infection:
    - Create CA-MRSA skin and soft tissue infections (e.g. "MRSA-SSTIs") using the following conditions identified at either T_0 or at the time of the ATF event:
        - Cellulitis identified via ICD-9 codes 528.3, 614.3, 681 & 682
        - Necrotizing fasciitis via ICD-9 codes 728.86
        - Pyomyositis via ICD-9 code 728.0
        - Gas gangrene via ICD-9 code 040.0
        - Impetigo via ICD-9 code 035
        - Abscess ICD-9 codes: 254.1, 478.1, 478.2, 522.0, 522.5, 522.7, 527.3, 528.3, 528.5, 529.0, 566, 611.1, 616.3, 616.4, 685.0
    - Determine the number of patients with potential MRSA-SSTIs: **303**

7. Type of Antibiotic Prescriber:
    - Create the variable fp_prec at T_0 where:
        - Fm_presc =0 if code is not 00 or 39
        - Fm_presc =1(labeled family physician or "FPs") if codes 00 or 39

Exposure: Excess Weight

1. Excess Weight
    - Create "obese" variable: if BMI $\geq$ 30 then "ob"=1 else ob=0
    - Create "overweight" variable: if $25 \leq$ BMI < 30 then ovwgt=1 else ovwgt=0
    - Create "normal weight" variable: if $18.5 \leq$ BMI < 25 then norwgt=1 else norwgt=0

2. Lack of Weight-Based Dosing
    - For those receiving an oral antibiotic prescription at T_0:
        - Create the variable "DD" each individual at T_0 using:

$$\left(\frac{\text{total number of pills}}{\text{duration of prescription in days}}\right) \times \text{dosage per pill in mg} = \text{daily dose in mg (DD)}$$