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Research Article

Hospital Antibiotic Wasting and Evaluation of Potential Ecologic Effects

Abstract

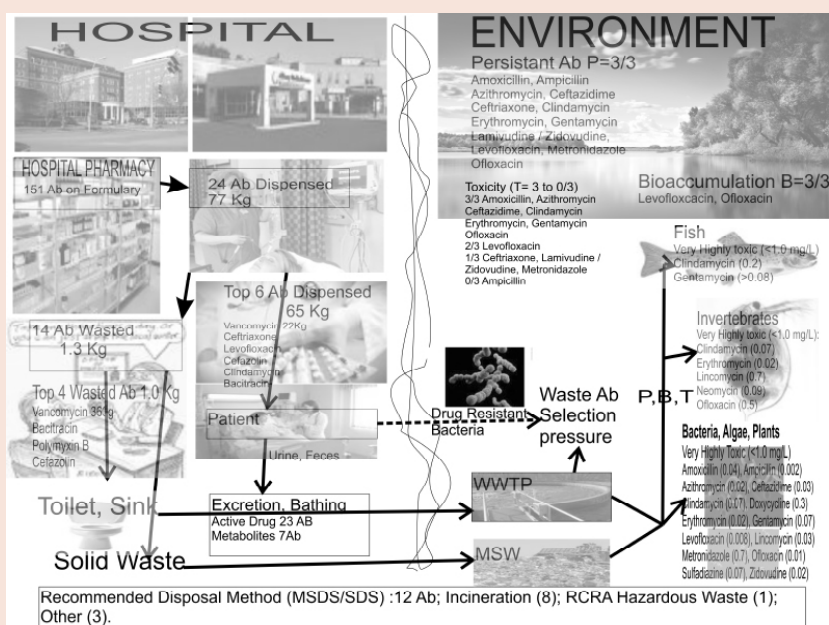
Drugs in wastewater arise from direct disposal by healthcare facilities among many other sources. We report the wasting of antibiotics (Ab) dispensed at 2 hospitals in Albany, NY during a 2 year period. We consider drug metabolism, excretion, disposal and toxicity to aquatic organisms in strategies for reducing antibiotic waste and impacts on bacterial resistance.

Drug records (12,345) from August, 2008 through April, 2009 included: numbers of drugs dispensed, returned and wasted. Overall, 77 kg of Ab were dispensed but only 1.3 kg were wasted. Six Ab (bacitracin, cefazolin, ceftriaxone, clindamycin, levofloxacin and vancomycin) accounted for 85% (66 kg) of drug dispensed; vancomycin (22 kg) was the most dispensed. Drug wasting as a percent of drug dispensed averaged 1.7% but varied widely. Almost one-half (45%) of the polymyxin B dispensed as a topical ointment was wasted or discarded. Only about 1.6% of vancomycin dispensed was wasted or discarded.

None of the top 4 wasted and only 3 of the top 6 dispensed Ab had Persistence, Bioaccumulation and Toxicity (PBT) Index values or environmental risk ratio (PEC/PNEC) data available. Vancomycin was minimally toxic to invertebrates, fish or green algae. Bacitracin was the most toxic to invertebrates or fish. Cefazolin was essentially non-toxic to green algae. All of the wasted, discarded or dispensed Ab were excreted as parent compound in the urine and/or feces of human patients at levels of 10 - 100% of the administered dose.

In healthcare facilities, Ab are disposed by wasting into water or other receptacles. We recommend returning excess drugs to the hospital pharmacy for incineration as the recommended method of disposal. Ab use and dispensing should be monitored according to recognized guidelines of antimicrobial stewardship. Knowledge of the adverse impacts from the release of highly toxic drugs into the environment must influence Ab selection and disposal.

Graphical Abstract





Abbreviations

AMCH: Academic Medical Center Hospital; ASTER: Assessment Tools for the Evaluation of Risk. United States Environmental Protection Agency http://www.epa.gov/med/prods_pubs/aster.htm; Last accessed 8/20/15; B: Bioaccumulation is the general term describing a process by which chemicals are taken up by an organism either directly from exposure to a contaminated medium or by consumption of food containing the chemical. US Environmental Protection Agency. Solid waste and emergency response glossary—Bioaccumulation <http://www.epa.gov/oswer/riskassessment/glossary.htm#b>; Last accessed 8/20/15; BOD: Biological Oxygen Demand is the amount of dissolved oxygen needed by aerobic biological organisms in a body of water to break down organic material present in a given water sample at a certain temperature over a specific time period; COD: Chemical Oxygen Demand is the standard method for indirect measurement of the amount of pollution (that cannot be oxidized biologically) in a sample of water; EC₅₀: Effective Concentration producing an adverse effect in 50% of a test species; EbC₅₀ or ErC₅₀: EC₅₀ in terms of reduction of growth rate; EyC₅₀: EC₅₀ in terms of change in biomass yield; Ecosar: Ecologic Structure Activity Relationships is a computerized predictive system that estimates aquatic toxicity. The program estimates a chemical's acute (short-term) toxicity and chronic (long-term or delayed) toxicity to aquatic organisms such as fish, invertebrates, and plants by using computerized Structure Activity Relationships (SARs). <http://www.epa.gov/oppt/newchems/tools/21ecosar.htm>. Last accessed 8/20/15; EPA: United States Environmental Protection Agency; FDA: United States Food and Drug Administration; IC₅₀: Half maximal inhibitory concentration (IC₅₀) is a measure of the effectiveness of a substance in inhibiting a specific biological or biochemical function; LC₅₀: Lethal Concentration producing 50% mortality in test species; MIC: Minimum Inhibitory Concentration (MIC) is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation; MSDS: Material Safety Data Sheet; Since 2009, known as SDS or Safety Data Sheet; Neutral Organics QSAR: Subset of chemicals within Ecosar Suite; OECD: Organization for Economic Cooperation and Development; P: Persistence is the length of time a substance resides in the environment; PBT: Persistence, Bioaccumulation, Toxicity index (<http://www.janusinfo.se>); PEC: Predicted Environmental Concentration; PNEC: Predicted No Effect Concentration, highest concentration of a substance that does not have a harmful effect in the environment; PNN: Probabilistic Neural Network modeling; QSAR: Quantitative Structure Activity Relationship; REACH: Registration, Evaluation and Authorization of Chemicals legislation of the European Union; SAR: Structure Activity Relationship; SCC: Surgical Care Center; STP: Sewage Treatment Plant; T or iT: Toxicity or Inherent Toxicity is the hazard a substance presents to the environment or human health; TSDF: Treatment, Storage and/or Disposal Facility for processing of chemical wastes;

Background

Healthcare drug wasting is a significant environmental, financial and public health concern [1]. Trace levels of antibiotics (Ab), endocrine disruptors, psychotropics, anti-inflammatory and

mood altering drugs have been detected in wastewaters, surface waters, and drinking water supplies for major world cities [2-8]. Drug residues have been found in tissues of aquatic organisms [9]. Pharmaceuticals are introduced into the aquatic environment from a variety of sources, such as: hospitals [10,11]; wastewater [12]; drug manufacturers [13,14], livestock, animal feeding operations and veterinary facilities [15-17]. Excessive dispensing and improper disposal of pharmaceuticals results in inflated healthcare costs and contamination of the environment [10,11].

Antibiotic/antimicrobial (Ab) drugs are but one important class of pharmaceutical and personal care products found contaminating the environment from a wide variety of sources. These drugs are prescribed to treat disease in animals, including humans, and to enhance growth of livestock and aquaculture. As a group, they are some of the most prescribed pharmaceuticals [18]. Adverse effects on the environment may arise from overuse and improper disposal of antibiotic/antimicrobial drugs leading to the emergence and dissemination of Ab resistant organisms [19]. Ab can be toxic to natural bacterial communities, impede organic matter degradation and disrupt bacterial nitrification/denitrification processes [20-22]. Ab are thus considered a priority risk group due to their high toxicity to bacteria and algae at low concentrations and their potential to initiate resistance amongst natural bacterial populations [23].

Many Ab are not completely metabolized or retained in the body and much of the active drug is excreted unchanged into the waste system [24,25]. Studies conducted on water quality in various countries have detected a number of antibiotics in the low µg/L or parts per billion range. Ab have been reported in surface water, groundwater, sediment, and soil [18,26-32].

In a prior publication [33], the patterns of wasting and potential environmental effects of propofol and other surgical drugs (e.g. atracurium, atropine, bupivacaine, ephedrine, epinephrine, lidocaine, proparacaine and succinylcholine) were reported from a surgical care center in Albany, NY. Of interest was how a small change in availability (e.g., removal of 50 and 100 mL propofol) reduced propofol wastage from 29.2 to 2.8 mL/day/bin. In a second communication [34], wasting of 15 controlled substance from two hospitals in Albany, New York were evaluated over a two year period, finding 3 (acetaminophen-codeine, fentanyl and midazolam) contributed nearly 90% of the total waste. The present study reports on the dispensing and wasting of selected antibiotics (Ab) given to patients at two health care facilities in Albany, NY over a nearly two year period. The study considered drug metabolism, excretion, disposal and toxicity to aquatic organisms (ecotoxicity). Strategies for antibiotic waste minimization and impacts on bacterial resistance from healthcare facilities are discussed.

Materials and Methods

As part of a pharmaceutical waste reduction pilot program, a total of 12,345 drug records for dispensing and waste collection were reviewed over a two year period (2008 and 2009) from two hospitals in Albany, NY. There were 4,889 automated drug dispensing machine (PYXIS®) records which were collected and tabulated for a one week period in April 2009 at the Albany Medical Center Hospital (AMCH);

630-bed, acute care) and 7,257 PYXIS® records from the South Clinical Campus (SCC; 20 bed surgical care center) from August 2008 through February 2009. Additionally, the contents of 199 pharmaceutical waste collection containers placed at SCC were sorted by hand and their contents tabulated.

Data were recorded by location, medication form, weight and number of units dispensed, returned, “bedside wasted” or discarded (e.g., a 1g dose of cefazolin was recorded as 1g regardless of the total weight of the drug formulation.). No human subject or patient identifier information was accessed; all data were recorded as summary aggregates. The funding agency (EPA) did not participate in the design, conduct, or analysis of the study. All numeric data were entered and archived on a Windows® based personal computer and analyzed by standard software packages (Microsoft Access®, Excel®).

N.b., Bedside wasted at health care facilities refers to the discharge of excess drug withdrawn for patient administration but only partially given to a patient. The leftover medication was then discarded by a healthcare professional who documented the wasting in the medication record.

Persistence, bioaccumulation, toxicity (PBT), environmental risk ratio (<http://www.janusinfo.se>), and ecotoxicity (<http://www.msdsonline.com>) were summarized for each drug wasted or discarded and displayed in **Table 1** and **Supplemental Table 1**.

Table 1 (and **Supplemental Table 1**) provides laboratory-derived acute toxicity information (< 96 hours). Acute inhibitory and lethal concentration data were considered to be the same for our review (e.g., $EC_{50} = IC_{50} = LC_{50}$). In all cases, the EC_{50} , IC_{50} , and LC_{50} value was selected from the data as it represents the most reproducible point on the dose-response curve.

In addition to the laboratory derived toxicity information presented in the MSDS/SDS and outside literature, mathematically modeled values are provided in **Table 1** (and **Supplemental Table 1**): Aster (http://www.epa.gov/med/prods_pubs/aster.htm), ECOSAR (Ecological Structure Activity Relationships – <http://www.epa.gov/oppt/newchems/tools/21ecosar.htm>), Neutral Organics QSAR (Quantitative Structure Activity Relationship), Oasis Forecast M, PNN, and Topkat [35-37].

Pharmacokinetic data (metabolism, conjugation and excretion) are summarized in **Table 2** (and **Supplemental Table 2**) from official government drug monographs and labels (Drugs@FDA; <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>) and the Hazardous Substances Data Bank, United States National Library of Medicine TOXNET Toxicology Data Network (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>).

For those drugs for which no data (designated as ND) were found for PBT, environmental risk ratio, ecotoxicity or pharmacokinetics, a computerized search of the available primary literature was done (<http://www.ncbi.nlm.nih.gov/pubmed>) and referenced in footnotes to **Tables 1, 2** (and **Supplemental Tables 1,2**).

Results

Antibiotics wasted or dispensed

As shown in **Figure 1**, a total of 1316 g of 14 antibiotic/antimicrobial

(Ab) drugs were wasted and discarded. Four Ab (vancomycin, bacitracin, polymyxin B and cefazolin) accounted for 1093 g (83%) of the total discarded/wasted drugs. Vancomycin was the most wasted with 363 g, followed by bacitracin (335 g), polymyxin B (222 g) and cefazolin (173 g; **Figure 1**). Vancomycin was also the most dispensed (22,059 g) of the 24 Ab given to patients at AMCH and SCC (**Figure 2**). Five other Ab (ceftriaxone, levofloxacin, cefazolin, clindamycin, and bacitracin) plus vancomycin accounted for over 80% (65,697 g of 77,108 g) of all of the antimicrobial drugs given to patients (**Figure 2**).

Drug wasting as a percent of drug dispensed averaged 1.7% but varied widely. Almost one-half (45%) of the polymyxin B dispensed as a topical ointment was wasted or discarded. Only about 1.6% of vancomycin dispensed was wasted or discarded (see **supplemental Figure 3**).

PBT and Environmental Risk Ratio (PEC/PNEC) of Healthcare Ab

As depicted in **Table 1** none of the top 4 wasted and only 3 (ceftriaxone, clindamycin and levofloxacin) of the top 6 dispensed Ab have PBT index values or environmental risk ratio (PEC/PNEC) data available. PBT index values for the 3 Ab averaged 6.0 and ranged from 4 of 9 (ceftriaxone) to 8 of 9 (levofloxacin). All three are very persistent (P value 3 of 3). Only levofloxacin is very bioaccumulative (B value 3 of 3). Ceftriaxone and clindamycin are not bioaccumulative (B value 0 of 3) but are “very highly toxic” (T value 3 of 3). Levofloxacin is “highly toxic” (T value 2 of 3). Environmental risk ratio (PEC/PNEC) for ceftriaxone is considered insignificant, ceftazidime is low and clindamycin is considered “Cannot Be Excluded” (**Table 1**).

Ecotoxicity Potential of Healthcare Ab Dispensed or Wasted to the Aquatic Environment

Vancomycin, the most wasted and dispensed Ab, was minimally toxic (48, 96 h LC_{50} from 264 mg/L to >1000 mg/L) to invertebrates, fish or green algae based solely on computer model data for ecotoxicity (**Table 1**). Bacitracin was the most toxic of the top 4 wasted Ab to invertebrates (*Daphnia* 48 h EC_{50} 30 mg/L; *Artemia* 48 h EC_{50} 22 mg/L) or fish (96 h LC_{50} 74 mg/L) based on MSDS and published data. Cefazolin was essentially non-toxic (48 & 96 h LC_{50} >1000 mg/L) to invertebrates, fish or green algae based on literature values and computer model data for ecotoxicity.

Of the top six dispensed Ab (vancomycin, ceftriaxone, levofloxacin, cefazolin, clindamycin, and bacitracin); clindamycin is very highly toxic to invertebrates (*Daphnia* 48 h EC_{50} <0.1 mg/L) and to fish (*Oryzias*, *Poecilia* 96 h EC_{50} <1.0 & 2.0 mg/L). Clindamycin and levofloxacin are very highly toxic (EC_{50} , IC_{50} or LC_{50} <1.0 mg/L) to algae and bacteria (**Table 1**). Levofloxacin has a 7d EC_{50} to *Microcystis* <0.01 mg/L.

Recommended disposal of Ab.

Incineration was recommended by the MSDS/SDS for ceftriaxone and clindamycin. Biological waste treatment was recommended for cefazolin. Vancomycin, bacitracin, polymyxin B, and levofloxacin had no method of disposal recommended by the MSDS/SDS.

Table 1: Summary of the Ecotoxic Potential of Antibiotic/Antimicrobial Drugs Dispensed and/or Wasted at an Academic Medical Center Hospital and at a Surgical Care Center in Albany, NY.

Antibiotic ^a Drug Generic Name CAS Number	Ecotoxicity ^b					
	PBT Score ^c	Risk ^d	Invertebrates	Fish	Other	Disposal ^e
Antibiotic / Antimicrobial Drugs Most Frequently (top 80%) "Wasted" and Discarded						
Vancomycin 1404-90-6 (VANCOCIN®)	ND ^f	ND	MSDS/SDS: ND Literature: ND = Predicted: <i>Daphnia</i> ^g LC ₅₀ ^h 264 mg/L 48h; mysid ⁱ LC ₅₀ >1000 mg/L 96h (Ecosar v1.11)	MSDS/SDS: ND Literature: ND = Predicted: Fish LC ₅₀ >1000 mg/L 96h; SW >1000 mg/L (Ecosar v1.11)	MSDS/SDS: ND Biodegradation enhanced during ozonation [89,90]. = Predicted: Green algae EC ₅₀ ^k >1000 mg/L 96h (Ecosar v1.11); PNEC ^l 0.32 mg/L	MSDS/SDS: ND
Bacitracin 1405-87-4 (BACiIM®)	ND ^g	ND	MSDS/SDS: <i>Daphnia</i> EC ₅₀ 30 mg/L 48h. = Literature: <i>Daphnia</i> EC ₅₀ 126 mg/L 24h; 30 mg/L 48h [76]; LC ₅₀ 34 mg/L 48h [77]; <i>Artemia</i> ^l EC ₅₀ 34 mg/L 24h & 22 mg/L 48h [78]. Predicted: ND	MSDS/SDS: ND Literature: <i>Salmo</i> ^m LC ₅₀ 74 mg/L 96h [77]. = Predicted: Fish >1000 mg/L (Neutral Organics QSAR)	MSDS/SDS, Literature, Predicted: ND	MSDS/SDS: ND
Polymyxin B 1405-20-5	ND	ND	MSDS/SDS, Literature, Predicted: ND	MSDS/SDS, Literature, Predicted: ND	MSDS/SDS, Literature, Predicted: ND	MSDS/SDS: ND
Cefazolin 25953-19-9 (ANCEF®)	ND	ND	MSDS/SDS, Literature: ND = Predicted: <i>Daphnia</i> LC ₅₀ >1000 mg/L; mysid LC ₅₀ >1000 mg/L 96h (Ecosar v1.11g)	MSDS/SDS, Literature: ND = Predicted: Fish LC ₅₀ >1000 mg/L 96h; SW >1000 mg/L (Ecosar v1.11); >1000 mg/L (PNN); >1000 mg/L (Neutral Organics QSAR)	MSDS/SDS: Measured oxygen demand: BOD ⁿ 23.4 mg/L; COD ⁿ 61,245 mg/L Literature: <i>Raphidocelis</i> ^o (<i>Pseudokirchneriella</i> or <i>Selenastrum</i>) EC ₅₀ >1000 mg/L 72h [79]. = Predicted: Green algae EC ₅₀ >1,000 mg/L (Ecosar v1.11)	MSDS/SDS: Biological waste treatment
Additional Most Frequently dispensed (Top 80%) Antibiotic / Antimicrobial drugs						
Ceftriaxone 104376-79-6 (ROCEPHIN®)	4 (3,0,1)	Insignificant	MSDS/SDS: <i>Daphnia</i> EC ₅₀ >100 mg/L 48h. -----Literature, = Predicted: ND	MSDS/SDS: <i>Oncorhynchus</i> ^p LC ₅₀ >1000 mg/L. -----Literature, = Predicted: ND	MSDS/SDS: <i>Raphidocelis</i> (<i>Pseudokirchneriella</i> or <i>Selenastrum</i>) EbC ₅₀ ^s >100 mg/L 72 h; ErC ₅₀ >100 mg/L 72h; Activated sludge LC ₅₀ 10 mg/L Waste water containing traces of substance should not enter the municipal drainage system until the substance has been inactivated.	MSDS/SDS: Incinerate with flue gas scrubbing
Clindamycin 24729-96-2 (CLEOCIN®)	6 (3,0,3)	Cannot be excluded	MSDS/SDS: <i>Daphnia</i> EC ₅₀ 0.07 mg/L 48h. Literature: ND = Predicted: <i>Daphnia</i> LC ₅₀ 435 mg/L 48h; mysid LC ₅₀ 261 mg/L 96h (Ecosar v1.11)	MSDS/SDS: <i>Oryzias</i> ^t (juvenile) EC ₅₀ 0.24 mg/L 96h; <i>Poecilia</i> ^u (juvenile) EC ₅₀ 2 mg/L 96h. Literature: ND = Predicted: Fish LC ₅₀ >1000 mg/L 96h; SW >1000 mg/L (Ecosar v1.11)	MSDS/SDS: Avoid release to environment. <i>Raphidocelis</i> (<i>Pseudokirchneriella</i> or <i>Selenastrum</i>) IC ₅₀ ^v 0.07 mg/L 72h; Activated sludge IC ₅₀ 35 mg/L 30 min. Literature: ND = Predicted: Green algae EC ₅₀ 195 mg/L 96h (Ecosar v1.11)	MSDS/SDS: Chemical incinerator with afterburner and scrubber
Levofloxacin 100986-85-4 (LEVAQUIN®)	8 (3,3,2)	Insignificant	MSDS/SDS: <i>Daphnia</i> EC ₅₀ 320 mg/L 48h; LC ₅₀ >10 mg/L 48h Literature: ND = Predicted: ND	MSDS/SDS: <i>Pimephaleu</i> ^w LC ₅₀ >10 mg/L 7d; <i>Lepomis</i> ^x LC ₅₀ >950 mg/L 96h. Literature: ND = Predicted: ND	MSDS/SDS: <i>Raphidocelis</i> (<i>Pseudokirchneriella</i> or <i>Selenastrum</i>) EC ₅₀ 7.4 mg/L 72h; <i>Lemna</i> ^y EC ₅₀ 51 □g/L; <i>Microcystis</i> ^z EC ₅₀ 7.9mg/L. = Literature: <i>Raphidocelis</i> (<i>Pseudokirchneriella</i> or <i>Selenastrum</i>) EC ₅₀ 7.4 mg/L 3d; <i>Microcystis</i> EC ₅₀ 7.9 x 10 ⁻³ mg/L 5d; <i>Lemna m.</i> EC ₅₀ 0.05 mg/L 7d [80]; <i>Anabaena</i> ^{aa} EC ₅₀ 4.8 mg/L 72h [81]; <i>Lemna g.</i> EC ₅₀ (wet weight) 0.19 mg/L 7d [82]; <i>Vibrio</i> ^{bb} EC ₅₀ 1150 mg/L 30min [83]. = Predicted: PNEC 7.9x10 ⁻⁶ mg/L	MSDS/SDS: ND



A total of 12,345 drug records for dispensing and waste collection were reviewed from 2008 and 2009. There were 4,889 records for a one week period in April, 2009 at the 630 bed Albany Medical Center Hospital and 7,257 records from August, 2008 through February, 2009 for the 20 bed South Clinical Campus of Albany Medical Center. The contents of 199 pharmaceutical waste collection containers from August, 2008 through February, 2009 placed at SCC were sorted by hand and the results tabulated by location, medication form and weight of units discarded. Weights are for active ingredient, e.g., a 1g dose of cefazolin was recorded as 1g regardless of the total weight of the drug formulation. Predicted ecotoxicity values derived from computer programs (e.g., Aster, Ecosar, and Neutral Organics QSAR, Oasis Forecast M, PNN, Topkat, etc.) in excess of 1000 mg/L (100 mg/dL or 0.1%) are recorded as >1000 mg/L

- a. Antibiotic drug: includes: anti-infective, anti-viral, anti-parasitic and anti-microbial prescription pharmaceuticals used to treat human infectious disease.
- b. Ecotoxicity: from material safety data sheets (MSDSs), open literature or predicted from computer programs.
- c. PBT: persistence, bioaccumulation, and toxicity (0 – 3 range for each, with zero being the most benign).
- d. Risk: ratio of PEC / PNEC where PEC/PNEC <0.1 = “insignificant”; PEC/PNEC is 0.1–1 = “low”; PEC/PNEC is 1–10 = “moderate”; and if the PEC/PNEC is >10 = “high”. Drugs are listed as “cannot be excluded” if insufficient evidence exists to reach a numeric ratio.
- e. Disposal: from MSDS, does not apply to consumers or end users.
- f. ND: no data available.
- g. *Daphnia*: crustacean, also known as (aka) “water flea” – all *Daphnia* referenced in Table 1 are *magna*, unless otherwise specified.
- h. LC₅₀: lethal concentration that kills 50% of the test organisms – acute toxicity.
- i. Mysid: crustacean, “mysid shrimp”.
- j. Predicted: modeled values for ecotoxicity as reported in Ecosar Volume 1.11 or in the OECD CCRWEB (<http://webnet.oecd.org/CCRWEB/Search.aspx> last accessed 3/12/14). OECD. Ecological categorization results from the Canadian domestic substance list. Paris, France: Organisation for Economic Co-operation and Development.
- k. EC₅₀: concentration of a material which is expected to cause an adverse biological effect on 50% of the test organisms (e.g. impede movement or growth) – acute toxicity.
- l. PNEC: Predicted No Effect Concentration, highest modeled concentration of a substance that does not have a harmful effect in the environment.
- m. *Salmo*: Fish, “salmon” or “trout”.
- n. *Artemia*: Crustacean, “brine shrimp”.
- o. BOD: Biochemical Oxygen Demand is the amount of dissolved oxygen needed by aerobic biological organisms in a body of water to break down organic material present at a certain temperature over a specific time period.
- p. COD: Chemical Oxygen Demand is the standard method for indirect measurement of the amount of pollution (that cannot be oxidized biologically) in a sample of water.
- q. *Raphidocelis* aka *Pseudokirchneriella* or *Selenastrum*: green algae.
- r. *Oncorhynchus*: fish, “salmon” or “trout”.
- s. ErC₅₀ or EbC₅₀ means EC₅₀ in terms of reduction of growth rate.
- t. *Oryzias*: fish, Ricefish.
- u. *Poecilia*: fish, “guppy” or “molly”.
- v. IC₅₀: inhibitory concentration (IC₅₀) is a measure of the effectiveness of a substance in inhibiting a specific biological or biochemical function 50% of the time – acute toxicity.
- w. *Pimephales*: fish, “fathead minnow”.
- x. *Lepomis*: fish, “sunfish”.
- y. *Lemna*: Vascular plant, “duckweed”.
- z. *Microcystis*: blue green algae.
- aa. *Anabaena*: blue green algae.
- bb. *Vibrio*: luminescent gram negative bacteria.

Metabolism and excretion of Ab

As depicted in Table 2, all of the “wasted”, discarded or dispensed Ab were excreted as parent compound in the urine and or feces of human patients at levels up to 90 - 100% of the administered dose. Three (ceftriaxone, clindamycin and levofloxacin) of these Ab underwent metabolism *in vivo* and active metabolites were formed from clindamycin. Only levofloxacin formed potentially reversible drug conjugates (predominantly glucuronides) which were excreted in the urine, feces or underwent enterohepatic recirculation (Table 2).

Discussion

The present communication found that only 1.3 kg of Ab was wasted (of 77 kg dispensed) at two hospitals in Albany, New York over a two year period. Others have reported higher levels of wasting of antibiotics and pharmaceuticals from healthcare facilities [10-12,38-39]. In previous studies [33,34], wasting of propofol and other injectable drugs or controlled substances (CS) was much higher (e.g., 41 liters of propofol emulsion, other liquid injectable surgical drugs and 8.5 kg of CS) from the same facilities reported herein. This disparity between Ab wasting and other pharmaceuticals may be attributable to the longstanding process of antibiotic stewardship [40]. Although originally promulgated to combat the rising phenomena of bacterial

resistance and decreasing efficacy of drug treatments for microbial diseases [41-44], these guidelines for antimicrobial stewardship could be applied to other classes of pharmaceuticals and lead to reductions in drug dispensing, drug wasting and environmental contamination [45]. This would supplement the process for lower dose prescribing advocated by Daughton and Ruhoy [1].

In the present study, we wished to determine which Ab contribute the greatest weight of waste. We find that both wasting and dispensing were amenable to application of the “Pareto Principle” also known as the 80–20 rule [46]. We have previously applied this to propofol and controlled substances [33,34] while others have applied this to hospital processes [47-49]. In the present study, vancomycin was the most frequently wasted or discarded (0.4 kg) and dispensed (22 kg) Ab at the AMCH and SCC. Six other Ab’s (bacitracin, polymyxin B, cefazolin, ceftriaxone, levofloxacin, clindamycin) together represent over 85% by weight of the Ab wasted/discharded or dispensed at AMCH and SCC. Others have found the top Ab discarded by weight vary widely by the facility studied or by the country of origin [12,38-39,50]. Thus each facility must determine its own profile of Ab wasting to direct the most effective Ab waste reduction plan.

Vancomycin is a powerful first line Ab and it is associated with

Table 2: Summary of the Metabolism and Excretion of Antibiotic / Antimicrobial Drugs Dispensed and / or Wasted at an Academic Medical Center Hospital and a Surgical Care Center in Albany, NY.

Antibiotic ^a Drug Generic Name CAS Number TRADE NAME [®] is included for illustrative purposes	Metabolism - Excretion ^b			
	Metabolism ^c	Active Metabolites ^d	Excretion of Parent Compound ^e	Drug Conjugates (glucuronides) Excreted ^f
Vancomycin 1404-90-6 (VANCOCIN [®])	N ^g	N	Y ^h (75%) ^j	ND ⁱ
Bacitracin 1405-87-4 (BACIIIM [®])	ND	ND	Y (fecal and 10 – 40% urine)	ND
Polymyxin B 1405-20-5	ND	ND	Y	N
Cefazolin 25953-19-9 (ANCEF [®])	N	N	Y (100%)	N
Ceftriaxone 104376-79-6 (ROCEPHIN [®])	Y	N	Y (33-67%)	ND
Clindamycin 24729-96-2 (CLEOCIN [®])	Y [84].	Y [84].	Y (10% Urine, 3.6% – Feces) [85].	ND
Levofloxacin 100986-85-4 (LEVAQUIN [®])	Y (<5%) ^j	ND	Y (87%)	Y [96].

A total of 12,345 drug records for dispensing and waste collection were reviewed from 2008 and 2009. There were 4,889 records for a one week period in April, 2009 at the 630 bed Albany Medical Center Hospital and 7,257 records from August, 2008 through February, 2009 for the 20 bed South Clinical Campus of Albany Medical Center. The contents of 199 pharmaceutical waste collection containers from August, 2008 through February, 2009 placed at SCC were sorted by hand and the results tabulated by location, medication form and weight of units discarded. Weights are for active ingredient, e.g., a 1g dose of cefazolin was recorded as 1g regardless of the total weight of the drug formulation.

- Antibiotic drug: includes: anti-infective, anti-viral, anti-parasitic and anti-microbial prescription pharmaceuticals used to treat human infectious disease.
- Metabolism — Excretion: data are summarized from official government drug monographs and labels Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>); DailyMed (<http://dailymed.nlm.nih.gov/dailymed/about.cfm>), RxList (http://www.rxlist.com/drugs/alpha_a.htm), Drugs.com (<http://www.drugs.com/>) and the Hazardous Substances Data Bank, United States National Library of Medicine TOXNET Toxicology Data Network (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>). Where data were insufficient, a search of the primary literature was conducted.
- Metabolism: indicates the drug undergoes change in the body.
- Active Metabolites: indicates the drug is changed in the body to pharmacologically active compounds prior to excretion, thus the risk to the environment from the excreted drug may reside in its metabolites and not in the parent compound.
- Excretion of Parent Compound: indicates that the drug, or a portion of the dose, is excreted unchanged.
- Drug Conjugates (glucuronides) Excreted: indicates excretion (urine or feces) of drug as conjugate.
- N: no.
- Y: yes.
- Value within parentheses: the percent of the drug that is excreted unchanged or the percent of the drug that is metabolized unchanged. Y (fecal and 10 – 40% urine) indicates that some fraction of the drug is excreted in the feces unchanged and from 10 to 40% of the drug is also excreted in the urine unchanged. Y (<5%) indicates that less than 5% of the drug is metabolized, more than 95% is not].

ND: not determined, no data available.

induction of vancomycin - resistant enterococci (VRE) bacteria [51,52]. As shown in this publication, a dearth of ecotoxicity data for vancomycin is available either from the manufacturer or in the open literature. Given that this Ab is the most wasted as well as most frequently dispensed, vancomycin should be a high priority for ecotoxicity investigations. Interestingly, 75% of a vancomycin dose is excreted without significant *in vivo* metabolism, production of active metabolites or formation of glucuronides, so efforts to limit vancomycin dispensing as well as wasting would be needed to reduce hospital discharges to the environment.

One goal of the present study was to test whether sources of ecotoxicologic information, readily available to healthcare environmental professionals, would be helpful in assessing the environmental impact of drug wasting/dispensing practices [53-58]. Unfortunately, we could find no “silver bullet”.

Persistence [59], is an important quality of an environmental contaminants harmful potential. For Ab, long lived residues provide a continuing selection pressure for antimicrobial resistance [60,61]. Similarly, bioaccumulation [62,63], is a function of amplification within the environment and indirectly is seen with increasing concentrations. In the present study none of the top wasted Ab were rated for persistence (P) or bioaccumulation (B) while of the top 6 dispensed Ab, 3 were rated as persistent and only one (levofloxacin) was bioaccumulative.

The toxicity component of the PBT index (Stockholm County Council, 2014) is based on the results of OECD Tests 201, 202 and 203 [64-66]. In the present study, we found clindamycin to be scored very highly toxic with levofloxacin and ceftriaxone of high to moderate toxicity respectively.

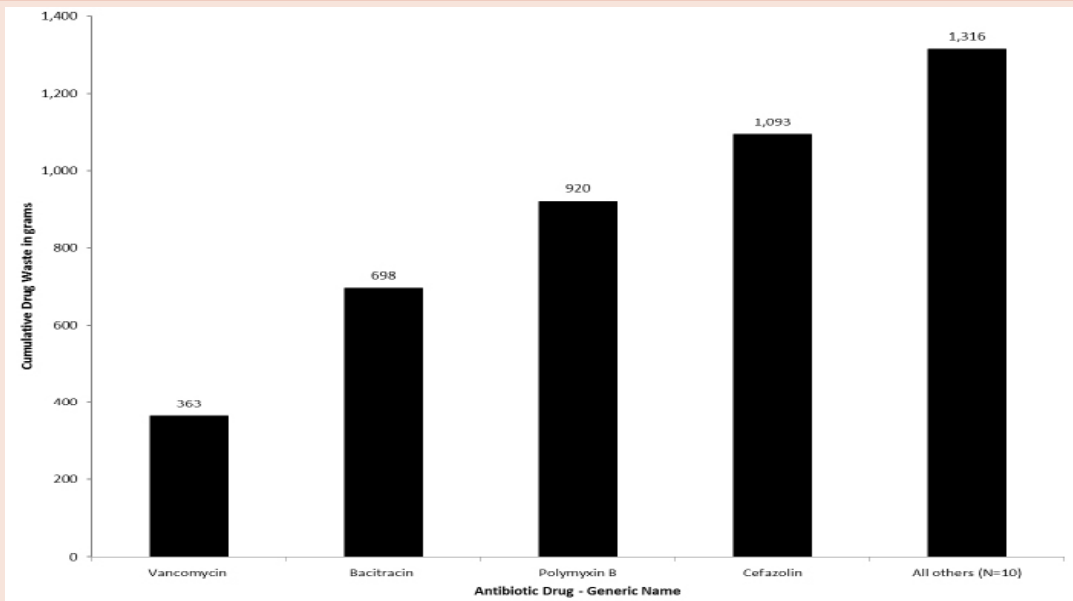


Figure 1: Bar graph of cumulative antibiotic drug waste (in grams) from two healthcare facilities over two years (2008-2009). A total of 12,345 drug records for dispensing and waste collection were reviewed from 2008 and 2009. There were 4,889 records for a one week period in April, 2009 at the 630 bed Albany Medical Center Hospital and 7,257 records from August, 2008 through February, 2009 for the 20 bed South Clinical Campus of Albany Medical Center. The contents of 199 pharmaceutical waste collection containers from August, 2008 through February, 2009 placed at SCC were sorted by hand and the results tabulated by location, medication form and weight of units discarded. Weights are for active ingredient, e.g., a 1g dose of cefazolin was recorded as 1g regardless of the total weight of the drug formulation. N.B., Antibiotic drug includes: anti-infective, anti-viral, anti-parasitic and anti-microbial prescription pharmaceuticals used to treat human infectious disease. In this study, four drugs accounted for over 80% of the drug waste.

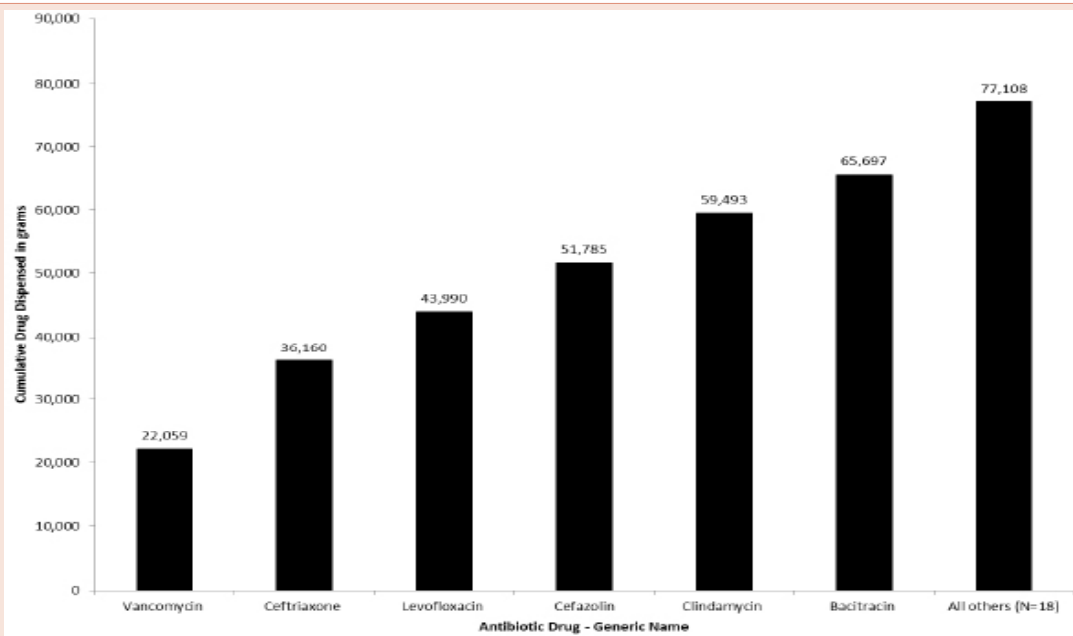


Figure 2: Bar graph of cumulative antibiotic drugs dispensed (in grams) from two healthcare facilities over two years (2008-2009). A total of 12,345 drug records for dispensing and waste collection were reviewed from 2008 and 2009. There were 4,889 records for a one week period in April, 2009 at the 630 bed Albany Medical Center Hospital and 7,257 records from August, 2008 through February, 2009 for the 20 bed South Clinical Campus of Albany Medical Center. The contents of 199 pharmaceutical waste collection containers from August, 2008 through February, 2009 placed at SCC were sorted by hand and the results tabulated by location, medication form and weight of units discarded. Weights are for active ingredient, e.g., a 1g dose of cefazolin was recorded as 1g regardless of the total weight of the drug formulation. N.B., Antibiotic drug includes: anti-infective, anti-viral, anti-parasitic and anti-microbial prescription pharmaceuticals used to treat human infectious disease. In this study, six drugs accounted for over 80% of the drug dispensed.

MSDSs are prepared by manufacturers for their products (for a more complete discussion of MSDS / SDS see the OSHA Hazard Communication Standard:

<http://www.osha.gov/dsg/hazcom/msdsformat.html>). Of the top 4 wasted Ab, only the MSDS for bacitracin reported a 48 h EC₅₀ of 30 mg/L. Of the top 6 dispensed Ab only 3 (ceftriaxone, clindamycin and levofloxacin) reported ecotoxicity data for *Daphnia*, fish and algae in the MSDS. Of these, clindamycin was very toxic to *Daphnia*, fish (*Oryzias* and *Poecilia*), and *Raphidocelis* algae. Levofloxacin the most toxic to *Lemna* (Duckweed - aquatic plant). As noted in our previous communication for controlled substances [34], we would recommend more complete aquatic toxicity laboratory data (e.g., EC₅₀ or LC₅₀ values for *Daphnia*, fish, algae and bacteria) be included in manufacturer MSDSs for the most frequently wasted/dispensed Ab drugs, rather than an over reliance on PBT or the environmental risk ratio.

In the present study, all of the Ab were excreted in whole or in part as active drug and/or drug conjugates. Kummerer [50], opined that for the Ab in use in Germany, overall 70% of Ab were excreted unchanged. As noted by others [67,68] our data suggest that for bacitracin, cefazolin polymyxin B and vancomycin, excretion of Ab from patients, with or without direct hospital wasting, would be the major source of these pharmaceuticals in hospital effluent. Unfortunately, little data are available in the open literature for wastewater concentrations of these Ab [11,69,70]. Based on the present study, we believe that the weight (grams) of Ab dispensed may be a more complete measure of contamination than grams of Ab recorded as wasted at bedside alone. This would not be true if the Ab studied were not excreted as active drug or as conjugates (primarily glucuronides) or if it were completely metabolized.

Disposal and destruction of Ab waste

Recommendations for disposal methods are confusing and conflicting [71-73]. Incineration is most commonly recommended for disposal of Ab by the MSDSs for the drugs examined in the current study. Of all of the Ab considered in this study, only sulfadiazine (Supplemental Table 1) meets the proposed criteria as a “hazardous waste pharmaceutical” requiring adherence to the proposed changes and additions to the Resource Conservation and Recovery Act (RCRA). These proposed rules [74], prohibit flushing and encourage incineration of pharmaceutical wastes. Seehusen and Edwards [75], surveyed disposal of medication practices and found incineration to be the best disposal option currently available. In any event, clear and detailed disposal recommendations are needed for all Ab and should be included in a manufacturer’s MSDS/SDS. This would provide guidance and clarity to healthcare environmental professionals and pharmacy staff alike in designing and implementing pharmaceutical waste programs. In the present study, drugs were discarded directly into pharmaceutical waste containers which were then sorted and shipped via commercial waste transporter to a permitted hazardous waste incineration facility (so called TSDF) and appropriate documentation maintained throughout.

Conclusions

The present communication extends and expands our earlier

observations on pharmaceuticals wasting from an acute care surgical hospital and an academic medical center in Albany, New York. We found a limited number of antibiotic / antimicrobial drugs accounted for the vast majority of Ab drug wasting, primarily vancomycin. For the Ab’s most frequently dispensed and wasted, environmental toxicity data including estimates of persistence, bioaccumulation and toxicity to aquatic organisms such as fish, bacteria and algae were sparse, conflicting and in some cases (vancomycin) absent. These Ab’s were in large measure excreted as active compounds in the urine and feces with the potential to facilitate drug resistance in organisms in the environment. Overall wasting of Ab’s appeared to be much less than expected based on our prior studies of surgical drugs and controlled substances, perhaps due to adherence to the principles of antibiotic stewardship. We conclude, in agreement with others [1], that extension of these guidelines [40-42], from Ab to all other drugs used in healthcare would result in significant reductions in drug wasting. We also conclude, in agreement with proposed USEPA guidelines [74], that waste drug disposal should not involve flushing but rather controlled and regulated incineration in commercial facilities as commonly recommended by the manufacturer’s MSDS.

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Supplemental Data

Supplemental Figure 1 depicts the cumulative drug waste in grams for 10 “other” Abs shown in Figure 1. Supplemental Figure 2 depicts the cumulative dispensing of the “other” 18 Ab shown in Figure 2. Supplemental Figure 3 depicts the percent of each Ab wasted over a two year period. Supplemental Table 1 summarizes the ecotoxicity data available for the other Ab wasted, discarded or dispensed not amongst the top Ab. Supplemental Table 2 depicts the human pharmacokinetic data available for the other Ab wasted, discarded or dispensed not amongst the top Ab.

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