The challenge of polypharmacy and drug interactions in old persons still needs an appraisal

Andrea Corsonello

(by Leonardo Pagani...do not shoot the piano player!)

ESCMID PGEC

Annecy, 2-3 October 2014

EVIDENCE BASED MEDICINE VS EVIDENCE "BIASED" GERIATRIC MEDICINE

Evidence "biased" geriatric medicine

- Older patients with comorbid conditions are frequently excluded from clinical trials, and evidence coming from these studies is only partly applicable to this population.
- This bias also affects clinical practice guidelines that are based on evidence coming from randomized trials and meta-analyses.
- Guidelines are generally disease-focused, thus raising the difficulties for applying them in older patients with comorbid conditions. Indeed, a guideline-driven therapeutic approach in such patients often results in adverse drug-drug or drug-disease interactions in the presence of complex polypharmacy regimens.

- T. Avni, S. Shiver-Ofer, L. Leibovici, E. Tacconelli, G. DeAngelis, B. Cookson, L. Pagani, M. Paul. Participation of elderly patients in randomized controlled trials addressing antibiotic treatment of pneumonia. *J Am Geriatr Soc 2014*; in press.
- **Antimicrobial trials including older complex patients are urgently needed.**

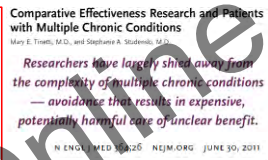
Outcomes

Efficacy studies
- Disease oriented
- Good for homogeneous populations
- Not reliable for complex patients

Effectiveness studies
- Universal health outcomes
- Real-world measure of clinical practice
- More informative
- More complex to be collected

The real patient is different from the ideal one

COMPLEXITY
- Multimorbidity
- Polypharmacy
- Functional status
  - Cognitive
  - Physical
  - Mood
- Incontinence
- Malnutrition
- Falls
- Osteoporosis


Comparative Effectiveness Research and Patients with Multiple Chronic Conditions

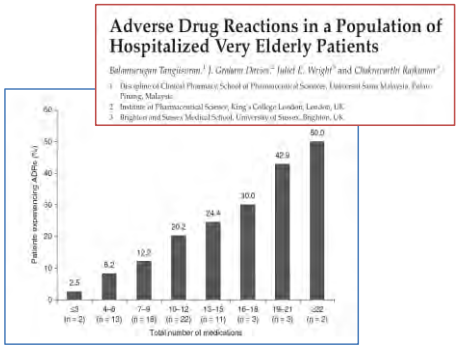
Mary E. Tinetti, M.D., and Stephanie A. Studenski, M.D.

Researchers have largely shied away from the complexity of multiple chronic conditions — avoidance that results in expensive, potentially harmful care of unclear benefit.

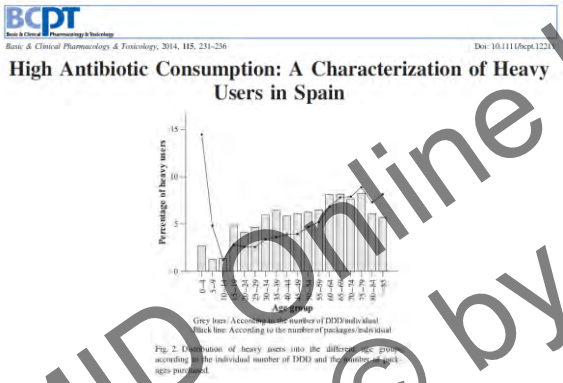
N ENGL J MED 364;26 NEJM.ORG JUNE 30, 2011

Concerns for older patients with polypharmacy regimens

- Phamacokinetics
- Pharmacodynamics
- Appropriate prescriptions
- Dosing in relation to kidney function



Drugs Aging 2012;29:669-679



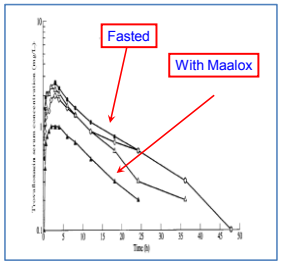
Pharmacokinetic parameters

- Absorption and Bioavailability: how much drug will be available (when given orally)
- Volume of distribution (Vd): where the drug distributes
- Protein binding: the unavailable fraction of a drug
- Half-life ($t_{1/2}$): how long the drug circulates
- Clearance: how the body clears the drug

Alterations in Absorption: Chelation

- Chelation
  - Irreversible binding of drugs in the GI tract
  - Tetracyclines, quinolones antibiotics - ferrous sulfate (Fe^{+2}), antacids (Al^{+3}, Ca^{+2}, Mg^{+2}), dairy products (Ca^{+2})
  - Usually separating administration of chelating drugs by > 2 hours decreases interaction effect

Trovafloxacin +/- Maalox



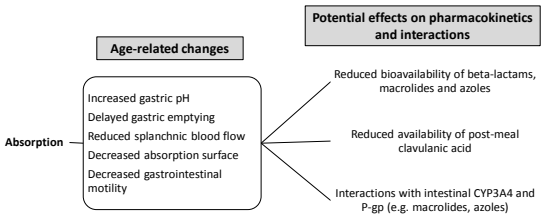
J Antimicrob Chemother 1997 Jun;39 Suppl B:93-7.

Age-related changes in PK

	Age related changes	Potential impact on interactions
Absorption	Increased gastric pH Delayed gastric emptying Reduced splanchnic blood flow Decreased absorption surface Decreased gastrointestinal motility	Increased risk of drug-induced esophageal lesions Changes in solubility and chemical stability of drugs Changes in tmax and Cmax Reduced active transport
Distribution	Changes in body composition Reduced protein binding sites Changes in blood-brain barrier permeability (?)	Increased volume of distribution for lipo-soluble drugs Reduced volume of distribution for water-soluble drugs Increased bioavailability of drugs displaced from protein binding sites
Metabolism	Reduced hepatic blood flow and overall liver mass Less effective first-pass metabolism and phase I metabolism Reduced CYPs activity (?)	Inhibition and/or induction of CYPs in the context of polypharmacy regimens
Excretion	Reduced kidney glomerular filtration rate and tubular secretion	Impaired elimination of water-soluble drugs

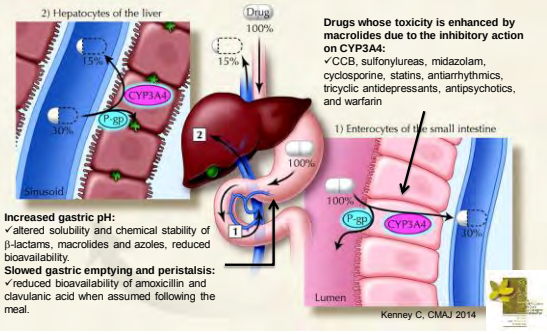
Corsonello et al. *under review*

Age-related changes in PK: *antibiotics*



Corsonello et al. *under review*

Age-related changes in PK: *antibiotics*

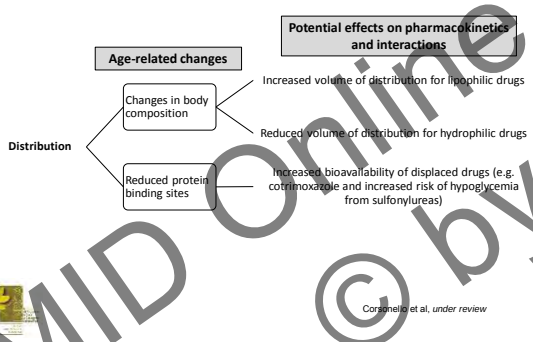


Drugs whose toxicity is enhanced by macrolides due to the inhibitory action on CYP3A4:
✓CCB, sulfonylureas, midazolam, cyclosporine, statins, antiarrhythmics, tricyclic antidepressants, antipsychotics, and warfarin

Increased gastric pH:
✓altered solubility and chemical stability of β-lactams, macrolides and azoles, reduced bioavailability.
Slowed gastric emptying and peristalsis:
✓reduced bioavailability of amoxicillin and clavulanic acid when assumed following the meal.

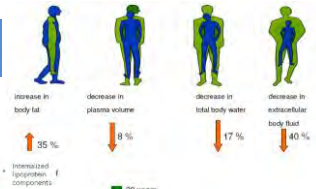
Kenney C, CMAJ 2014

Age-related changes in PK: *antibiotics*

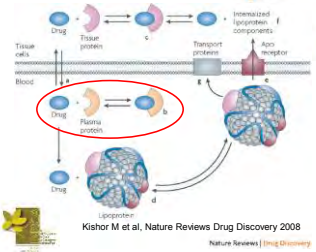


Corsonello et al, *under review*

Age-related changes in PK: *antibiotics*



Shi et al, CDM 2010



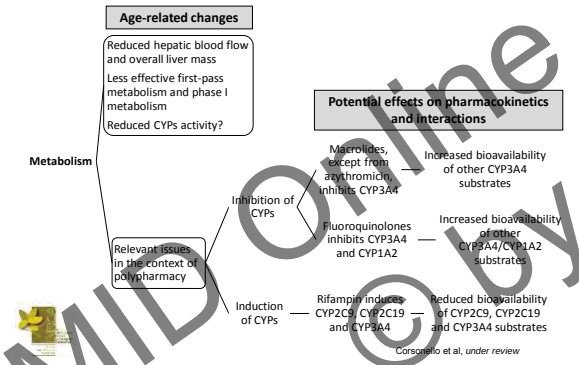
Kishor M et al, Nature Reviews Drug Discovery 2008

Protein binding interactions:
✓Cotrimoxazole is able to increase serum concentrations of methotrexate and sulphonylureas by displacing them from plasma protein binding sites, resulting in a clinically relevant increased risk of hypoglycemia and severe bone marrow depression, respectively.

Metabolism and aging

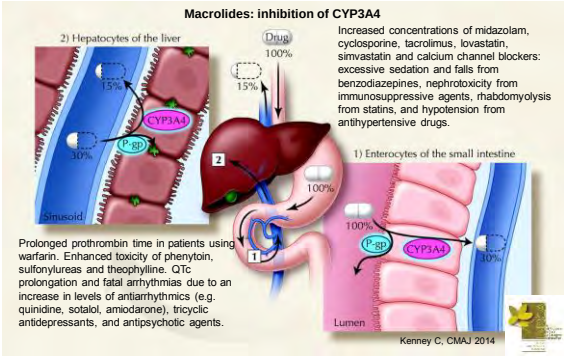
- Liver volume decreases up to 20-30% and hepatic blood flow is reduced 20-50%
- Reduced hepatic first-pass effect
  - Bioavailability of drugs undergoing extensive first-pass metabolism can be significantly increased
  - Biovailability of drugs that need to be activated in the liver may be significantly reduced
- Hepatic clearance of drugs with flow-limited metabolism may be reduced up to 40%

Age-related changes in PK: *antibiotics*



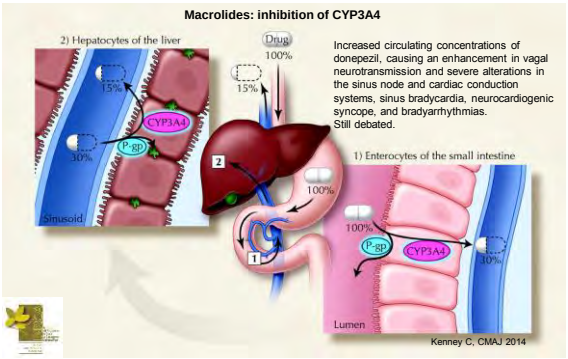
Corsonello et al, *under review*

Age-related changes in PK: *antibiotics*



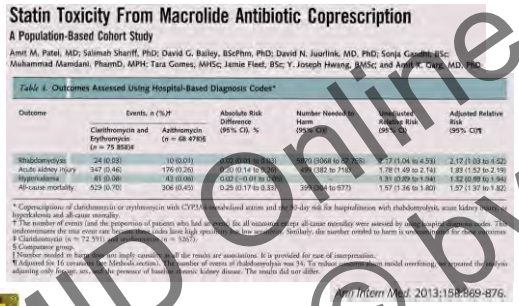
Kenney C, CMAJ 2014

Age-related changes in PK: *antibiotics*



Increased circulating concentrations of donepezil, causing an enhancement in vagal neurotransmission and severe alterations in the sinus node and cardiac conduction systems, sinus bradycardia, neurocardiogenic syncope, and bradyarrhythmias. Still debated.

Age-related changes in PK: *antibiotics*



Statin Toxicity From Macrolide Antibiotic Coprescription

A Population-Based Cohort Study

Amit M. Patel, MD; Salimah Shariff, PhD; David G. Bailey, BScPhm, PhD; David N. Juurlink, MD, PhD; Sonja Gandhi, BSc; Muhammad Mamdani, PharmD, MPH; Tara Gomes, MHSc; Jamie Fleet, BSc; Y. Joseph Hwang, BMSc; and Amit X. Garg, MD, PhD

Table 4. Outcomes Assessed Using Hospital-Based Diagnosis Codes*

Outcome	Events, n (%)†		Absolute Risk Difference (95% CI), %	Number Needed to Harm (95% CI)‡	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)¶
	Clarithromycin and Erythromycin (n = 75 858)§	Azithromycin (n = 68 478)§				
Rhabdomyolysis	24 (0.03)	10 (0.01)	0.02 (0.01 to 0.03)	5979 (3068 to 17 778)	2.17 (1.04 to 4.53)	2.12 (1.03 to 4.52)
Acute kidney injury	347 (0.46)	176 (0.26)	0.20 (0.14 to 0.26)	504 (382 to 718)	1.78 (1.49 to 2.14)	1.83 (1.52 to 2.19)
Hyperkalemia	81 (0.08)	43 (0.06)	0.02 (−0.01 to 0.05)		1.31 (0.89 to 1.94)	1.32 (0.89 to 1.94)
All-cause mortality	529 (0.70)	306 (0.45)	0.25 (0.17 to 0.33)	399 (304 to 577)	1.57 (1.36 to 1.80)	1.57 (1.37 to 1.82)

* Coprescriptions of clarithromycin or erythromycin with CYP3A4-metabolized statins and the 30-day risk for hospitalization with rhabdomyolysis, acute kidney injury or hyperkalemia and all-cause mortality.

† The number of events (and the proportion of patients who had an event) for all outcomes except all-cause mortality were assessed by hospital diagnosis codes. These underestimate the true event rate because these codes have high specificity but low sensitivity. Similarly, the number needed to harm is overestimated for these outcomes.

‡ Clarithromycin (n = 72 591) and azithromycin (n = 32 673).

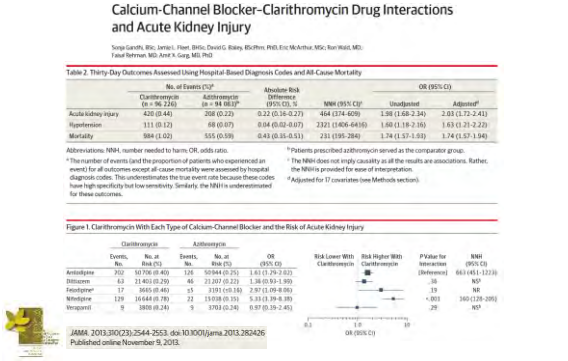
§ Comparator group.

‖ Number needed to harm does not imply causality as all the results are associations. It is provided for ease of interpretation.

¶ Adjusted for 16 covariates (see Methods section). The number of events of rhabdomyolysis was 34. To reduce potential ascertainment bias, model overfitting, we repeated the analysis adjusting only for age, sex, and the presence of baseline chronic kidney disease. The results did not differ.

Ann Intern Med. 2013;158:869-876.

Age-related changes in PK: *antibiotics*



Calcium-Channel Blocker–Clarithromycin Drug Interactions and Acute Kidney Injury

Sonja Gandhi, BSc; Jamie L. Fleet, BMSc; David G. Bailey, BScPhm, PhD; Eric McArthur, MSc; Ron Wald, MD; Yusuf Rehman, MD; Amit X. Garg, MD, PhD

Table 2. Thirty-Day Outcomes Assessed Using Hospital-Based Diagnosis Codes and All-Cause Mortality

	No. of Events (%)[a]		Absolute Risk Difference (95% CI), %	NNH (95% CI)[c]	OR (95% CI)	
	Clarithromycin (n = 96 226)	Azithromycin (n = 94 063)[b]			Unadjusted	Adjusted[d]
Acute kidney injury	426 (0.44)	208 (0.22)	0.22 (0.16–0.27)	464 (374–609)	1.98 (1.68–2.34)	2.03 (1.72–2.41)
Hypotension	111 (0.12)	68 (0.07)	0.04 (0.02–0.07)	2321 (1406–6416)	1.60 (1.18–2.16)	1.63 (1.21–2.22)
Mortality	584 (1.02)	555 (0.59)	0.43 (0.35–0.51)	231 (195–284)	1.74 (1.57–1.93)	1.74 (1.57–1.94)

Abbreviations: NNH, number needed to harm; OR, odds ratio.

[a] The number of events (and the proportion of patients who experienced an event) for all outcomes except all-cause mortality were assessed by hospital diagnosis codes. This underestimates the true event rate because these codes have high specificity but low sensitivity. Similarly, the NNH is underestimated for these outcomes.

[b] Patients prescribed azithromycin served as the comparator group.

[c] The NNH does not imply causality as all the results are associations. Rather, the NNH is provided for ease of interpretation.

[d] Adjusted for 17 covariates (see Methods section).

Figure 1. Clarithromycin With Each Type of Calcium-Channel Blocker and the Risk of Acute Kidney Injury

	Clarithromycin		Azithromycin		OR (95% CI)
	Events, No.	No. at Risk (%)	Events, No.	No. at Risk (%)	
Amlodipine	302	50 706 (0.40)	126	50 844 (0.25)	1.61 (1.29–2.02)
Diltiazem	63	21 401 (0.29)	46	21 207 (0.22)	1.38 (0.93–1.99)
Felodipine[a]	17	3665 (0.46)	≤5	3191 (≤0.16)	2.97 (1.09–8.06)
Nifedipine	129	16 644 (0.78)	22	15 018 (0.15)	5.33 (3.39–8.38)
Verapamil	9	3898 (0.24)	5	3703 (0.14)	0.97 (0.39–2.45)

Risk Lower With Clarithromycin | Risk Higher With Clarithromycin

0.5 1.0 10

OR (95% CI)

P Value for Interaction	NNH (95% CI)
[Reference]	661 (451–1223)
.16	NS[b]
.19	NR
<.001	360 (228–205)
.29	NS[b]

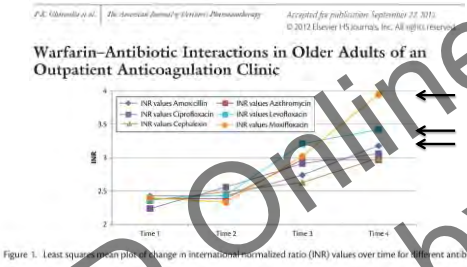
JAMA. 2013;310(23):2544-2553. doi:10.1001/jama.2013.282426
Published online November 9, 2013.

Age-related changes in PK: *antibiotics*

- Fluoroquinolones inhibit CYP3A4 and CYP1A2:
  - enhanced toxicity of several drugs, including:
    - Benzodiazepines
    - Fentanyl
    - Carbamazepine
    - Statins
    - Theophyline
    - Haloperidol
    - Warfarin

Corsonello et al, *under review*

Age-related changes in PK: *antibiotics*



Warfarin–Antibiotic Interactions in Older Adults of an Outpatient Anticoagulation Clinic

Figure 1. Least squares mean plot of change in international normalized ratio (INR) values over time for different antibiotics.

Renal drug clearance

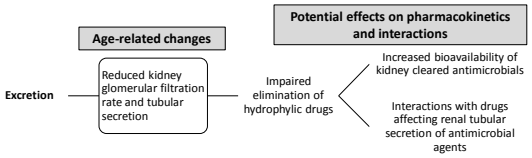
Glomerular filtration

Tubular secretion

Tubular re-absorption

20-25% cardiac output or 1.1 L/min goes to kidney
10% filtered in the glomerulus
Normal GFR is 120 ml/min for a 70 kg, 20-year-old man

Age-related changes in PK: *antibiotics*



Corsonello et al, *under review*

Preventing nephrotoxicity

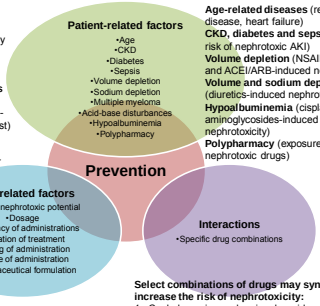
General preventing measures

- Adjust medication dosages to renal function
- Assess baseline renal function, and consider patient's renal function when prescribing a new drug.
- Avoid nephrotoxic combinations.
- Correct risk factors for nephrotoxicity before initiation of drug therapy.
- Ensure adequate hydration before and during therapy with potential nephrotoxins.
- Use equally effective non-nephrotoxic drugs whenever possible.

Shetz et al, Curr Opin Crit Care 2005
Munar & Singh, Am Fam Phys 2007
Naughton CA, AFP 2008
Bentley et al, Crit Care Med 2010
Logham-Adham et al, Expert Opin Drug Saf 2012
Bell et al, Austr Fam Phys 2013

Preventing nephrotoxicity

Nephrotoxic potential
Dose-dependent effect (mainly for drugs causing crystal deposition, tubular toxicity, and hemodynamic toxicity)
Frequency of administrations (aminoglycosides)
Route of administration (intra-arterial administration of contrast)
Pharmaceutical formulation (nephrotoxicity is lower with liposomal amphotericin than for amphotericin lipid complex)



Age-related diseases (renovascular disease, heart failure)
CKD, diabetes and sepsis (increased risk of nephrotoxic AKI)
Volume depletion (NSAID-induced and ACEI/ARB-induced nephrotoxicity)
Volume and sodium depletion (diuretics-induced nephrotoxicity)
Hypoalbuminemia (cisplatin- and aminoglycosides-induced nephrotoxicity)
Polypharmacy (exposure to multiple nephrotoxic drugs)

Shetz et al, Curr Opin Crit Care 2005
Munar & Singh, Am Fam Phys 2007
Naughton CA, AFP 2008
Bentley et al, Crit Care Med 2010
Logham-Adham et al, Expert Opin Drug Saf 2012
Bell et al, Austr Fam Phys 2013

Select combinations of drugs may synergistically increase the risk of nephrotoxicity:
1. Cephalosporins and aminoglycosides
2. Vancomycin and aminoglycosides
3. Cephalosporins and acyclovir

Age-related changes in PD

- Pharmacodynamics, defined as the biochemical and physiological effects of a drug at its site of action, is strictly related to several variables, such as:
  - the concentrations of the drug at the receptor
  - the interaction between the drug and its receptor (changes in receptor number, receptor affinity, second messenger response, and cellular response)
  - the homeostatic regulation
  - several patient-specific factors, including age, gender, ethnicity, genetics, polypharmacy and diseases

Guiding principles for antimicrobial use in older adults

- Stratify patient risk for severe infections and multidrug-resistant pathogens based on lifestyle and functional status.
- Provide early and empiric therapy using national guidelines and local antibiogram when available.
- Obtain complete medication history and carefully select antimicrobials to avoid severe drug-drug interactions and drug-disease interactions.
- Correctly reach maximal therapeutic doses of antimicrobials according to age-related changes in pharmacokinetic and pharmacodynamic parameters in order to avoid potential adverse effects.
- Discontinue antimicrobial therapy based on the patient's clinical status and identified pathogen.
- Perform clinical trials testing the use of antimicrobial agents in specific elderly populations.

Herring AR & Williamson JC, Clin Geriatr Med 2007

Interventions to improve appropriateness

Study	Setting and intervention	Evidence
Lutters et al, 2004	Geriatric hospital Educational intervention targeting prescribing physicians	Reduced consumption and costs of antibiotics
Liew et al, 2012	Hospital Antimicrobial stewardship programs	Reduce length of hospital stay and improved safety
Gonzales et al, 2004	Medicare office visits Educational intervention targeting patients and caregivers	Modest decline in antibiotic use for acute respiratory infections, but no substantial effect
Bedouch et al, 2009	Hospital, medical wards Computerized physician order entry (CPOE) system and pharmacists	Routine participation of clinical pharmacists in clinical medical rounds may facilitate identification of drug-related problems and enhance patient safety
Rivkin et al, 2011	Intensive care unit Interactions screening procedure guided by clinical pharmacist	Decreased number of clinically important interactions requiring therapy modification, and reduced length of stay
Buising et al, 2008	Emergency department Computerized decision support system	Improved antibiotic prescribing practices
Joosten et al, 2013	Ambulatory care setting Automatic renal function alerts (involving general practioners and community pharmacists)	A considerable proportion of the population is at risk for adverse drug events from antimicrobials due to impaired renal function. Providing renal function data to the pharmacists and physicians may help to adjust medication dosage.

Corsonello et al, *under review*

Antimicrobials stewardship programs

Table 2
Types of intervention recommended by the antimicrobial stewardship programme that may have an impact on morbidity and mortality ($N = 743$).

Intervention	Accepted [n (%)]*		Rejected [n (%)]*		P-value
	Total	Patients who died	Total	Patients who died	
De-escalation based on culture results	97 (16.8)	13 (2.2)	27 (16.4)	5 (3.0)	0.555
Discontinue antibiotic	270 (46.7)	32 (5.5)	86 (52.1)	11 (6.7)	0.851
Narrowing of empirical coverage	49 (8.5)	6 (1.0)	38 (23.0)	1 (0.6)	0.239
Intravenous-to-oral switch	162 (28.0)	4 (0.6)	14 (8.5)	1 (0.6)	0.346
Total	578/743 (77.8)	55 (9.5)	165/743 (22.2)	18 (10.9)	0.557

* Percentages are out of the total accepted or rejected, respectively; except where indicated.

sions in six departments. Shorter average length of stay (mean ± standard deviation 19.4 ± 19.9 days vs. 24.2 ± 24.2 days) was observed among patients of physicians who accepted ASP suggestions compared with patients of physicians who rejected ASP interventions ($P < 0.01$). ASP interventions did not alter all-cause mortality ($P = 0.191$). In addition, the number of infection-related re-admissions ($P < 0.001$) and the 14-day re-infection rate ($P = 0.009$) were higher among patients whose physicians rejected ASP interventions. In conclusion, interventions recommended by the ASP in SGH were safe and were associated with a reduction in the duration of hospital stay, 14-day re-infection rate and infection-related re-admissions.

Liew et al, Int J Antimicrobial Agents 2012

Antimicrobials stewardship programs

Antimicrobial Stewardship in Long-term Care Facilities

Susan M. Rhee, MD[a,*], Nimalie D. Stone, MD[b]

Infect Dis Clin N Am 28 (2014) 237–249
http://dx.doi.org/10.1016/j.idc.2014.01.001

SUCCESSFUL ANTIMICROBIAL STEWARDSHIP INTERVENTIONS IN LTCFS

Although still relatively new in LTCF settings, the impact of such an ASP has already demonstrated positive results. The implementation of such programs led to a 30% decrease in systemic antibiotic usage, both in oral and intravenous medications, in addition to a decrease in the rate of positive *C. difficile* tests, in one institution.[50] Although this study used an ID service, simply distributing appropriate educational material targeting the most common infections in LTCFs has shown to improve antibiotic usage, as demonstrated by Monette and colleagues.[51] a 20% decrease in prescriptions that were not adherent to guidelines was seen in the group of prescribers who were given the educational material, as opposed to control.

Areas of Future Needed Work

- Robust studies examining the efficacy of various programs and how they fit into individual facility types with differing resources.
- Attention to the issues of transmission between the LTCFs and the acute care facilities serving the same community.
- Increased implementation of the nationally available guidelines in LTCFs.

Approaching the conclusion..

- Age-related changes in pharmacokinetics and pharmacodynamics make drug therapy very challenging in older people.
- Polypharmacy and multimorbidity significantly contribute to the increased risk of adverse drug reactions and interactions.
- Trials investigating antimicrobials in complex older patients are urgently needed.
- In the meantime, educational interventions, antimicrobial stewardship, computer-assisted prescription and dosing in relation to kidney function may help to improve appropriateness and safety while reduce cost.