Antimicrobial Stewardship: Opportunity is Everywhere

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UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

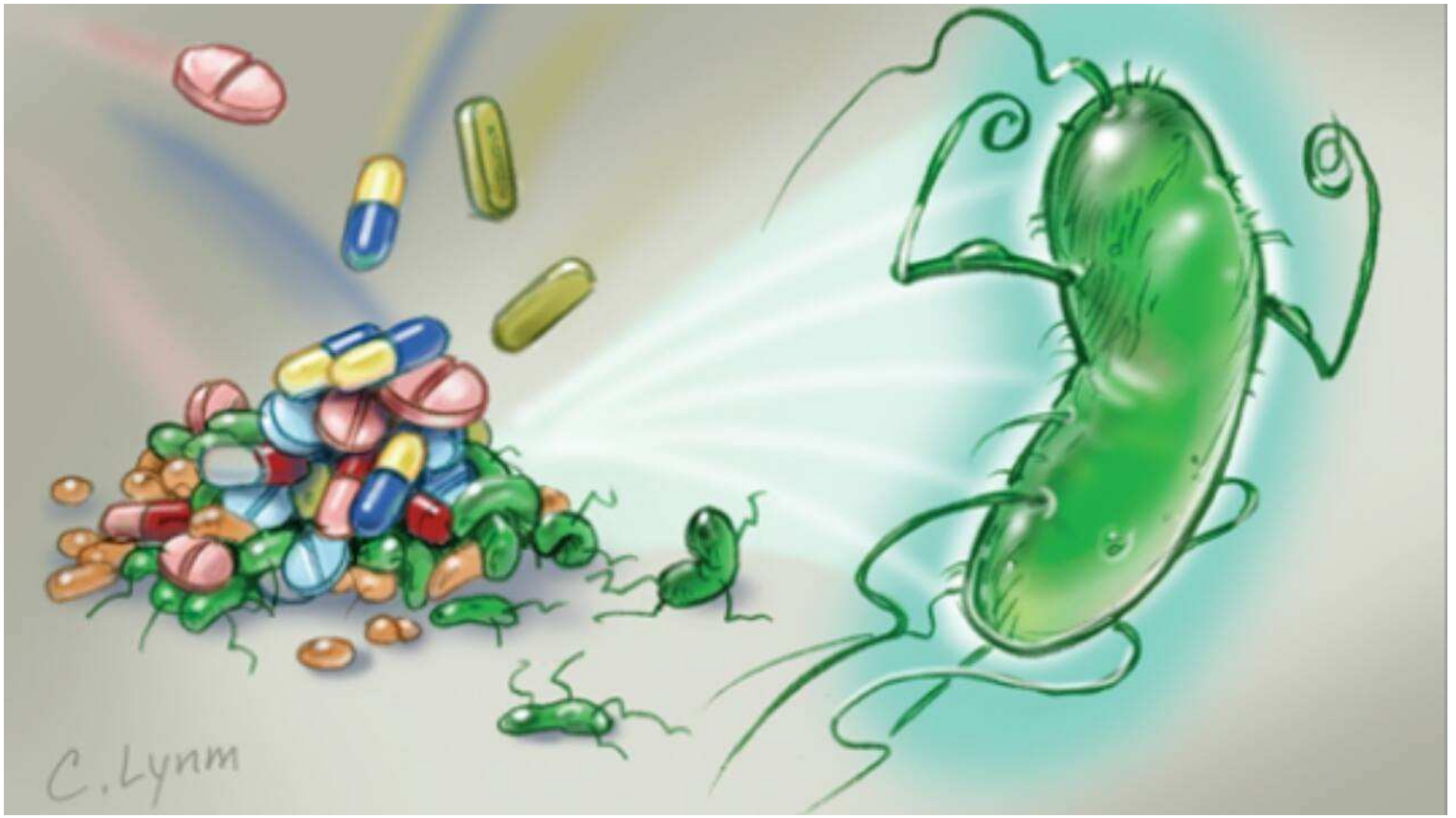
Presenter Disclosure

- I have no current or past relationships with commercial entities
- I will receive an honorarium from CSHP-NB for this learning activity

Learning Objectives

- Describe the impact of antimicrobial resistance on individuals & communities.
- Discuss the goals of Antimicrobial Stewardship Programs in hospitals.
- Identify opportunities to promote Antimicrobial Stewardship in your own practice, in the absence of or complementary to a formal program.

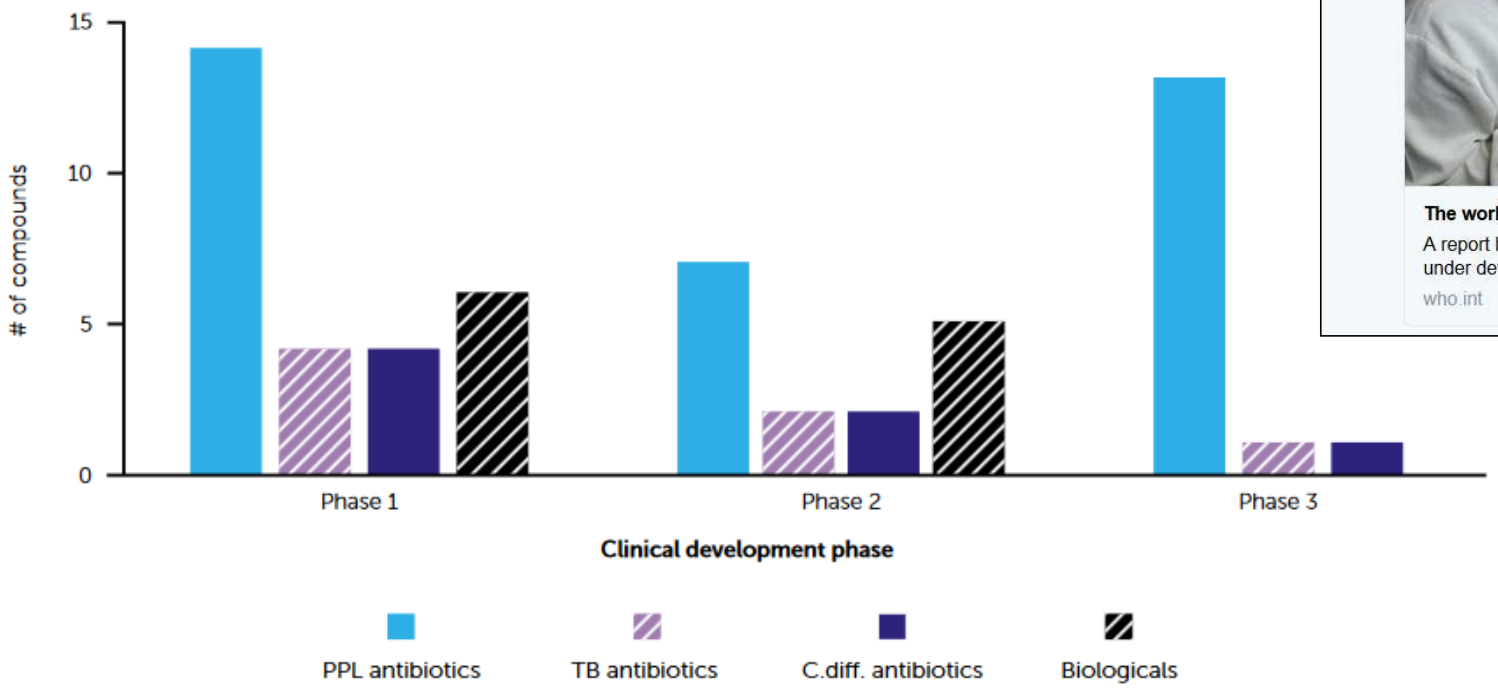
Antimicrobial Resistance



World Health Organization. Causes of Antibiotic Resistance (infographic). http://www.who.int/campaigns/world-antibiotic-awareness-week/infographics/en/; accessed 27-09-2017.
Punnoose AR, Lynm C, Golub RM. Antibiotic Resistance. *JAMA*. 2012;308(18):1934. doi:10.1001/jama.2012.6916.

WHO: 19 September 2017

Fig 1. Antibacterial agents currently in phases 1–3 of clinical development[a]



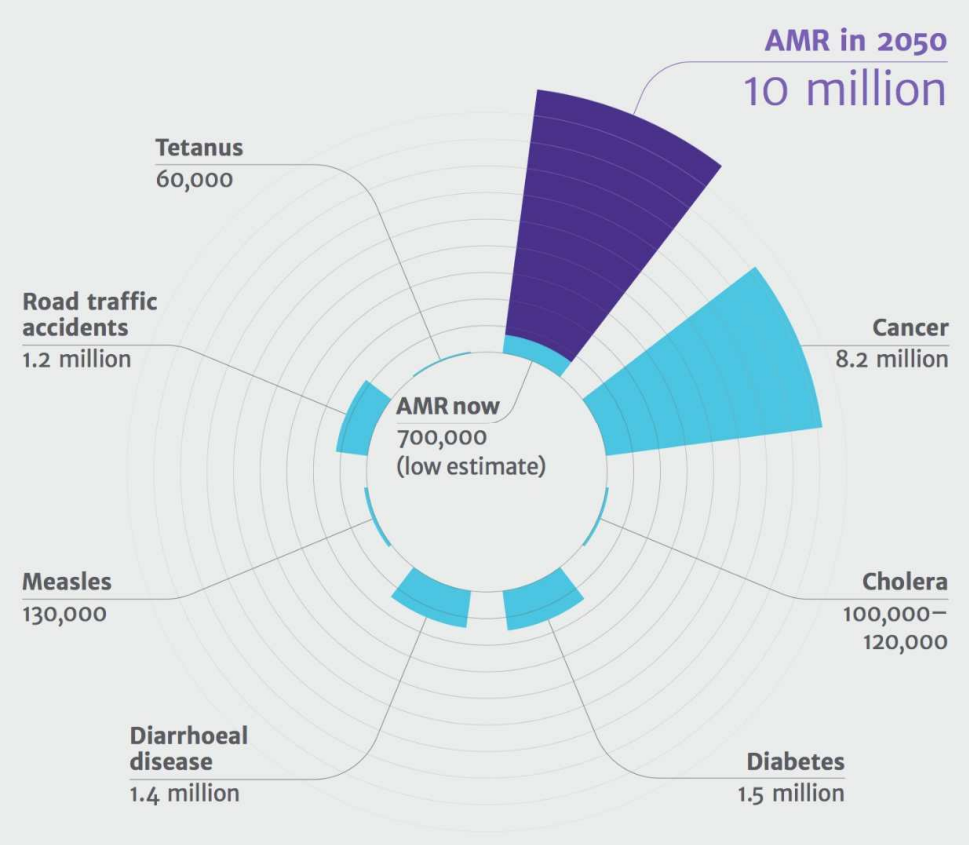
Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.11). Licence: CC BY-NC-SA 3.0 IGO.

Clear & Present Danger

- Impact on individuals
  - Increased risk of death
  - Prolonged lengths of stay
  - Higher rates of treatment failure
  - Non-AMR-related adverse consequences of antimicrobials
    - Common & rare-but-serious AE, incl. *C. difficile* infection
      - 20% of inpatients experience an AE[1]
    - Long-term effects on microbiome & human development?
- Impact on communities
  - Increased healthcare costs (est. $1 billion CDN per year)[2]
  - Plus lost productivity & income

Friedman ND, Temkin E, Carmeli Y. *Clin Microbiol Infect*. 2016:22(5):416.
[1]Tamma PD, Advic E, Xi D *et al*. *JAMA Intern Med*. 2017;177(9):1308.
[2]https://www.publichealthontario.ca/en/DataAndAnalytics/OntarioHealthProfile/Pages/OHP-IWR-AR.aspx; accessed 29-09-2017.

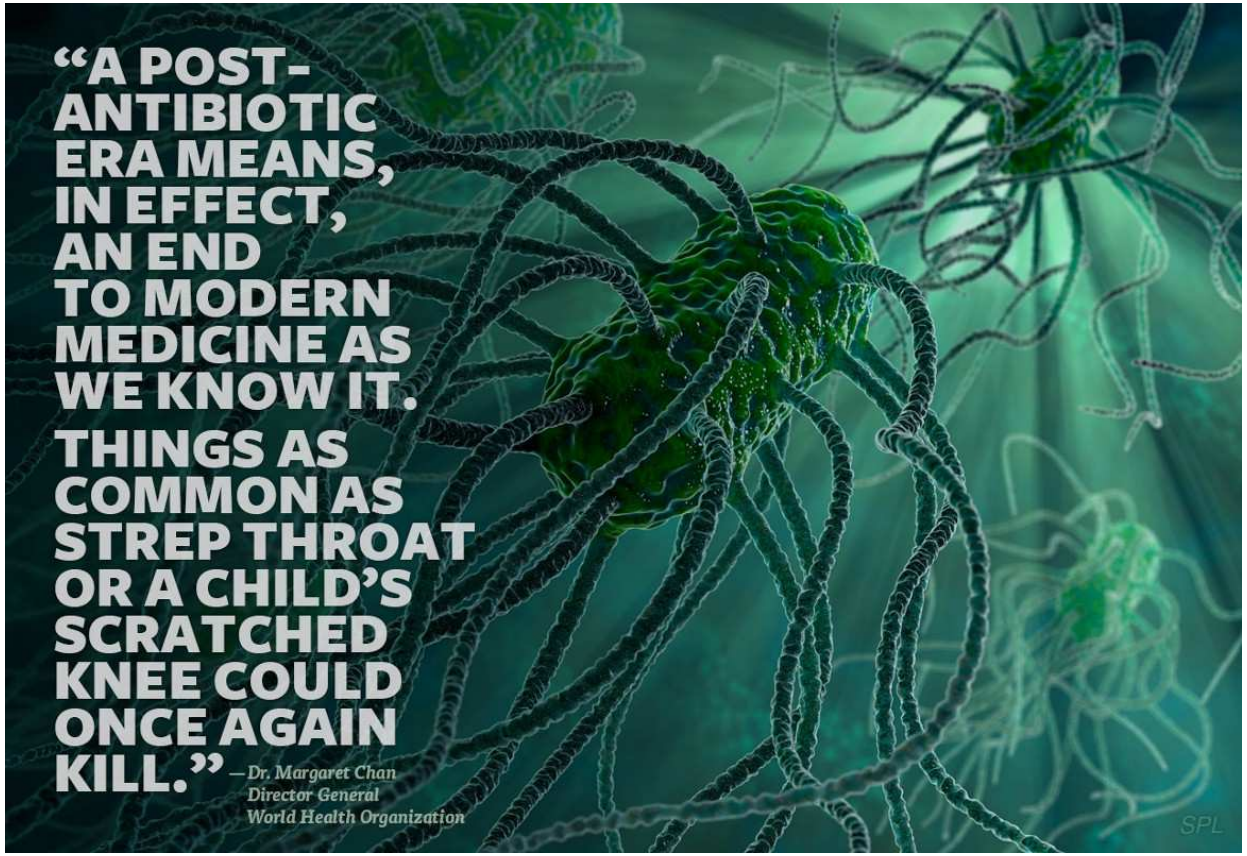
Global Impact of Antimicrobial Resistance



Decreased global GDP by up to 3.8%, resulting in up to 28.3 million more living in poverty

O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. *Rev Antimicrob Resist*. 2014. http://amr-review.org/Publications.
Adeyi O, Baris E, Jonas O *et al.* 2017. Washington, D.C. : World Bank Group. http://documents.worldbank.org/curated/en/323311493396993758/final-report.

2012: A Post-Antibiotic Era?



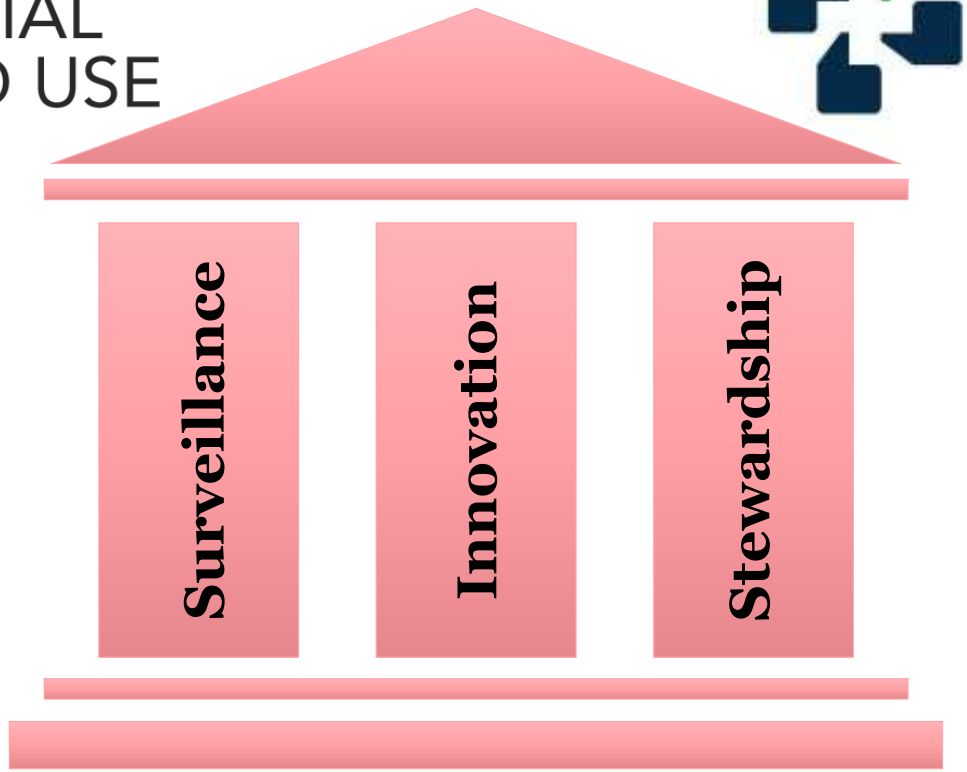
2016: Pan-R *K. pneumoniae* in Nevada

http://www.who.int/dg/speeches/2012/amr_20120314/en/; accessed 26-09-2017.
Chen L, Todd R, Kiehlbauch J, Walters M, Kallen A. *Notes from the Field*: Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae* — Washoe County, Nevada, 2016. MMWR Morb Mortal Wkly Rep 2017;66:33. DOI: http://dx.doi.org/10.15585/mmwr.mm6601a7.

FEDERAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE AND USE IN CANADA

BUILDING ON THE FEDERAL FRAMEWORK FOR ACTION

HealthCare*CAN*
Leading. Innovation. Together.



Public Health Agency of Canada. Federal Action Plan on Antimicrobial Resistance and Use in Canada. March 2015. https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/alt/pdf/publications/drugs-products-medicaments-produits/antibiotic-resistance-antibiotique/action-plan-daction-eng.pdf.
HealthCare*CAN*. Antimicrobial Stewardship in Canada: An issue brief submitted to parliament's standing committee on health. June 5, 2017. http://www.healthcarecan.ca/wp-content/themes/camyno/assets/document/GovSubmissions/2017/EN/HESA-AMS_EN.pdf.

Antimicrobial Stewardship in Hospitals

- "activity that includes appropriate selection, dosing, route & duration of antimicrobial therapy… to achieve the best patient outcomes, reduce the risk of infections, reduce or stabilize levels of antibiotic resistance, & promote patient safety"[1]
- ROP for inpatient acute, cancer, rehab & complex continuing
  - Variety of strategies (audit & feedback, formulary, education, order forms, guidelines/ clinical pathways, strategies for streamlining/ de-escalation, dose optimization & IV to po conversion)
- ALL antimicrobial use drives resistance
  - Focus on unnecessary &/ or suboptimal use (i.e. too broad, too long, too low, not needed at all)
  - Estimated to be up to 50% of all inpatient prescribing[2]

[1]Accreditation Canada. Required Organizational Practices: Handbook 2016. Accessed at https://accreditation.ca/sites/default/files/rop-handbook-2016-en.pdf; 23-02-2017.
[2]The Center for Disease Dynamics, Economics and Policy. (2015). *The state of the world's antibiotics 2015*. Washington, DC: Author.

Practicing Antimicrobial Stewardship as a Non-ID RPh

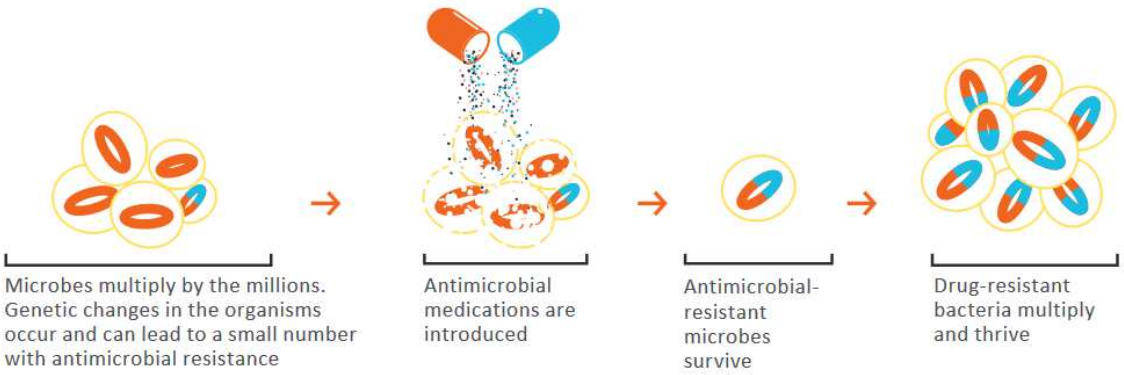
- Chances are, you already do!
  - Perform dose optimization
  - Operationalize IV to oral conversion
  - Encourage de-escalation based on cultures
  - Encourage use of clinical pathways & routine orders
  - Enforce formulary & “protected” antimicrobial policies
  - Participate in & provide education regarding best practices
  - Plus more…

Squeezing the Most Stewardship Out of Your Practice

- On admission
  - Ask about antimicrobials in the BPMH
  - Interrogate allergies
- At the time of prescribing
  - Encourage source control
  - Foster culturing stewardship
  - Question the infectious diagnosis
- At discharge
  - De-escalate
  - Define duration

Using the BPMH on Admission: Recent Antimicrobials

- Look & ask about antimicrobial use, even if not admitted for ID
  - Consider a specific area on your BPMH form to trigger & highlight



- Recent antimicrobial use increases chance of resistance (urine, resp)[1,2]
  - Highest risk within a month of therapy but some persist out to one year
  - Increased with number & duration of courses
  - Inconsistent evidence to determine if class matters

[1] Costelloe C, Metcalfe C, Lovering A *et al. BMJ*. 2010;340:c2096.
[2] Kuster SP, Rudnick W, Shigayeva A *et al. Clin Infect Dis*. 2014;59(7):944.
http://www.publichealthontario.ca/en/eRepository/OHP_infog_AntimicrobialResistance_2016.pdf; accessed 09-08-2016.

Beta-lactam Allergies

- ~10% report BL allergy; true incidence of IgE reaction closer to 0.05%[1]
  - False attribution secondary to viral rash, loss of antibodies over time
  - Late-onset T-cell-mediated exanthems occur in 2 to 12% & often do not preclude future use
  - True penicillin allergy shows cross-reactivity with cephalosporins in < 2 to 5%[2]
- Patients who report BL allergy
  - More likely to receive second-line therapies (less effective, more toxic, expensive & broad), even when history is not suggestive of acute hypersensitivity reaction[3]
  - Longer hospital stays, increased risk of *C. difficile*, MRSA & VRE infection[4]
- "In patients with a history of beta-lactam allergy, we suggest that ASPs promote allergy assessments & penicillin skin testing when appropriate"[5]

[1]Macy E. *Curr Allergy Asthma Rep*. 2014;14:476.
[2]Trubiano J, Adkinson NF, Phillips E. *JAMA*. 2017;318(1):82.
[3]Epstein R, St. Jacques P, Wanderer J *et al. A&A Case Reports*. 2016;6:263.
[4]Macy E, Contreras R. *J Allergy Clin Immunol*. 2014;133(3):790.
[5]Barlam T, Cosgrove S, Abbo L *et al. Clin Infect Dis*. 2016;62(10):e51.

BL Skin Testing: Coming Soon to an ASP Near You?

- Pragmatic multicenter prospective evaluation of POC BL skin testing in Toronto
  - Each site used trained ASP team members (pharmacists & at least one ID MD)
  - Informed consent by ID MD, skin test by ASP RPh & BL challenge by bedside RN
  - Addition of skin testing to PA&F (with detailed allergy history) resulted in
    - Significant increase in the use of preferred BL therapy
    - Significant decrease in the use of fluoroquinolones and carbapenems
    - No difference in infection related readmission/ death, LOS or adverse drug reactions
- Challenges to wide-spread application
  - Availability of training & onsite ID MD
  - Workload (1hr at bedside & clinical reassessment 4hrs after challenge administered)

Leis J, Palmay L Ho G *et al. Clin Infect Dis*. 2017. doi: 10.1093/cid/cix512.

Using the BPMH on Admission: Allergy Assessment

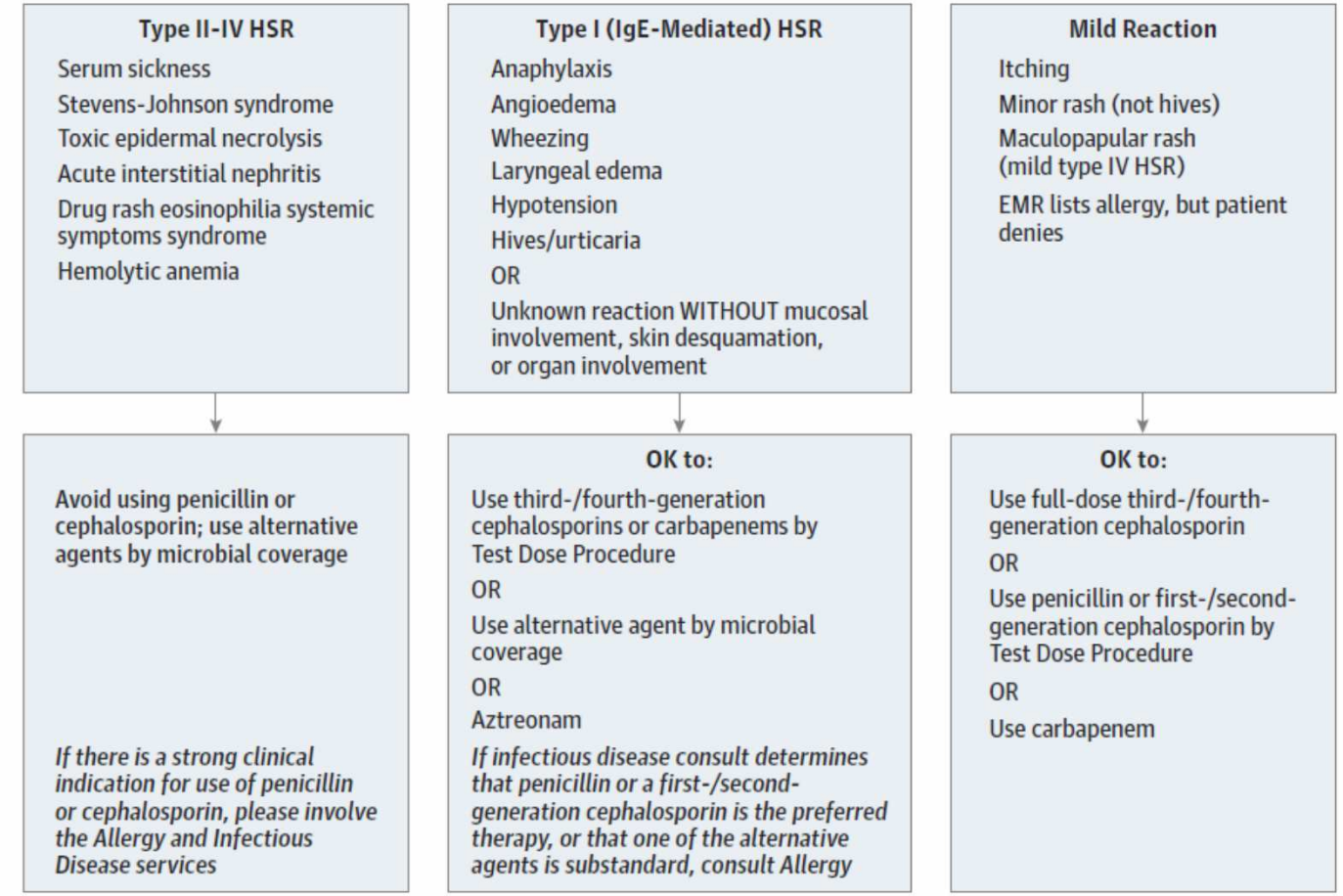
- Ask
  - RPh-led BL allergy interview lead to successful switch in 65% cases[1]
- Tell
  - Explain to patient difference between allergy & AE & risks associated with mislabeling
- Document
  - Document details of discussion/ in-hospital reaction/ results of any challenges & share with colleagues outside of hospital
- Refer
  - Any patient who is denied BL therapy should be considered for skin testing as an outpatient

Standardized allergy interview questions

1.	Do you remember the specific antibiotic that you had a reaction to? If so, what antibiotic was it?
2.	Can you describe the reaction that you experienced? If so, what happened?
3.	Did you require medical treatment for the reaction (antihistamines, epinephrine, hospitalization, etc.)?
4.	How soon after taking the medication did you experience a reaction?
5.	Did the reaction occur more than 10 years ago?
6.	Were you taking any other new medications at the time of reaction? If so, have you tolerated them since?
7.	Since having your initial reaction, have you tolerated a penicillin or cephalosporin (e.g., amoxicillin, Augmentin, or Keflex)?
8.	What antibiotics do you normally take when you get sick?

[1]Sigona N, Steele J, Miller C. *J Am Pharm Assoc*. 2016;56(6):665.

Figure. Penicillin Allergy Pathway for Antibiotic Prescription in Patients With Penicillin Allergy



Vaisman A, McCready J, Powis J. *JAMA Int Med*. 2017. doi: 10.1001/jamainternmed.2016.8185.

At the Time of Prescribing: Encourage Source Control

- Does something need to be drained?
  - In "pus under pressure", antimicrobials are an adjunct & symptoms will be prolonged
- Is it possible/ necessary to remove the IV line?
  - Although CLABSI risk is greater, consider PIV frequency[1]
- Is it possible to replace/ remove urinary catheter?
  - In CA-UTI, associated with quicker time to defervescence & better improvement at 72hs[2]
  - Recall limited appropriate indications[3] (great opportunity if doing bedside rounds)

[1]https://www.americannursetoday.com/piv/; accessed 28-09-2017.
[2]Raz R, Schiller D, Nicolle LE. *J Urol*. 2000;164:1254.
[3]https://choosingwiselycanada.org/hospital-medicine/; accessed 28-09-2017.

At the Time of Prescribing: Culturing Stewardship

- Ensure that cultures have been/ will be drawn before dose is administered
- Encourage strategies to minimize contamination/ colonization
  - Urinary catheters older than 2wks should be replaced
  - Ask if IDSA Guidelines for diabetic foot wound culture were/ can be adhered to[1]
  - Do not ask for test of cure for most infections
- A positive culture is NOT a diagnosis

Choosing Wisely Canada

  - Don't ask for cultures unless infection is clinically likely
    - i.e. foul smelling/ cloudy urine, chronic ulcers w/o evidence of infection
  - Question appropriateness of routine/ screening orders
    - Recent study found no association between preop bacteriuria & PJI or SSI[2]

[1]Lipsky BA, Berendt AR, Cornia PB *et al. Clin Infect Dis.* 2012:54(12):132.
[2]Honkanen M, Jamsen E, Karppelin M *et al. Clin Microbiol Infect.* 2017. doi: 10.1016/j.cmi.2017.07.022.

At the Time of Prescribing: Question the Infectious Dx

> **It's easy to prescribe antibiotics. It takes time, energy & trust not to do so.**

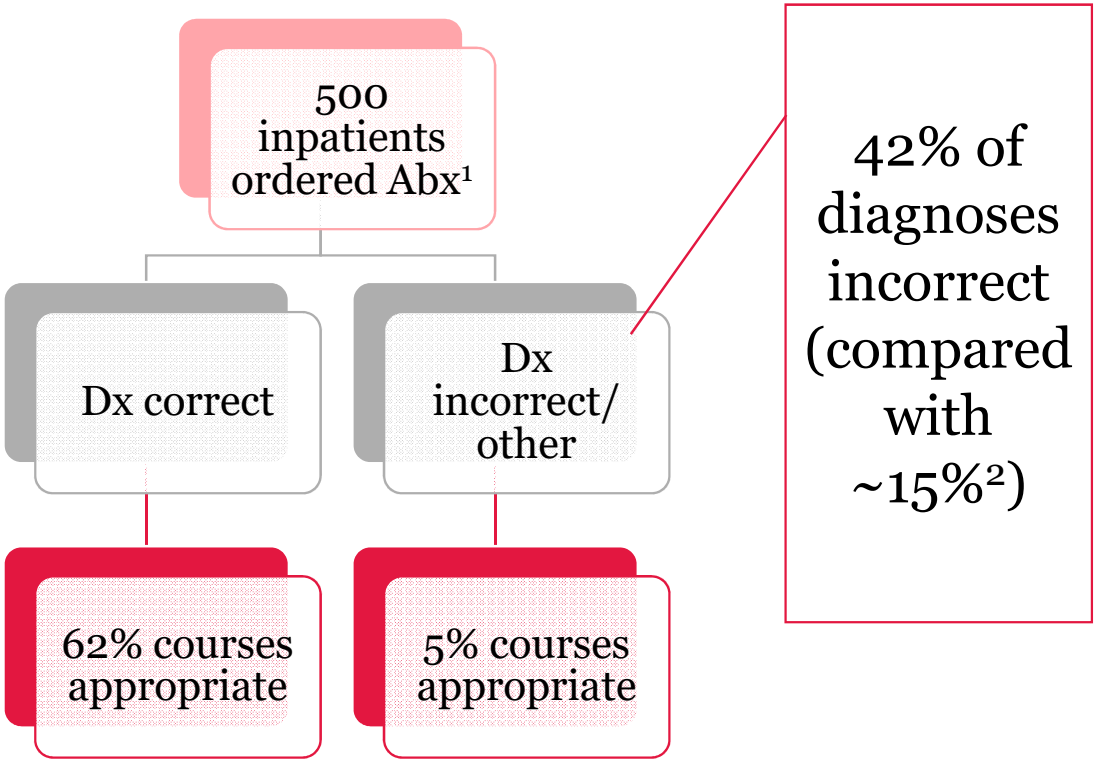
McCartney, M. *BMJ*. 2015;351:h4697.

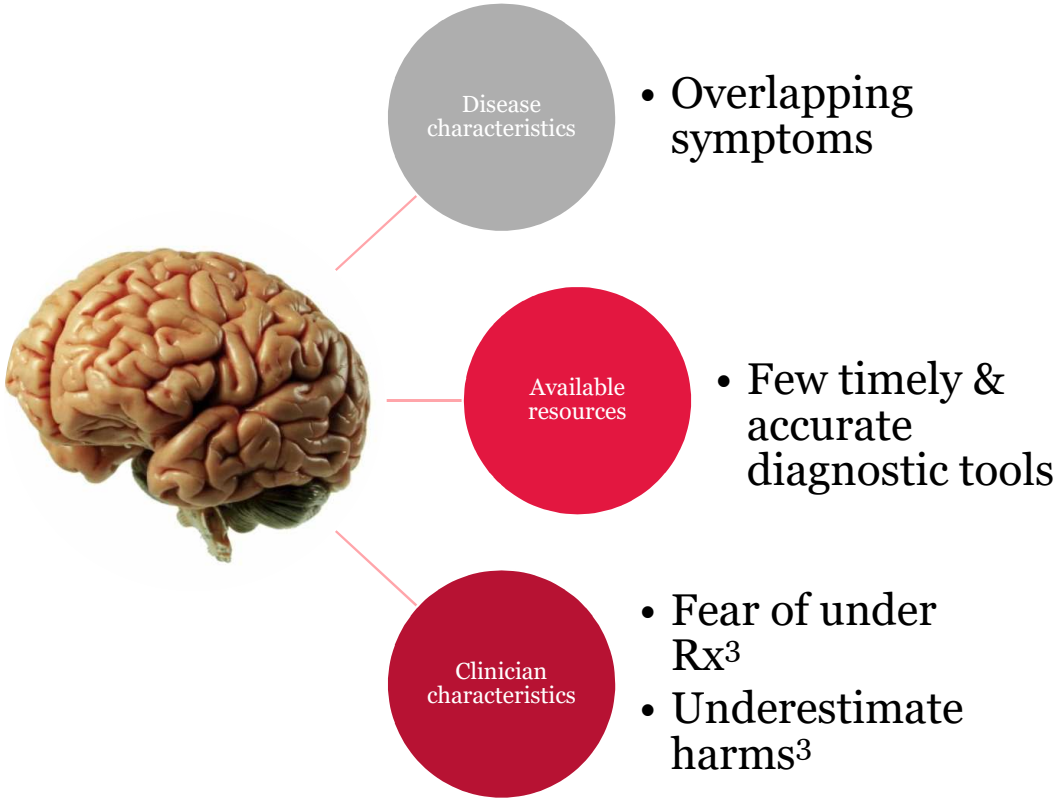
Psychology of Antimicrobial Use

- Systematic review of MD knowledge & beliefs about antimicrobial resistance[1]
  - Knew about it & believed it was a serious problem
  - However,
    - Considered it a distant consequence compared with possible proximal consequences of inaction
    - Blamed it on "others"
- More so than some other therapeutics, appears to be highly affected by superstition, ritual and professional etiquette[2]
  - "Defensive" / "Just in case" medicine – fear overpowers logic, antimicrobial acts as an anxiolytic (for MD, for family)

[1]McCullough AR *et al. J Antimicrob Chemother*. 2015; 70: 2465–2473. doi:10.1093/jac/dkv164.
[2]Broom A, Kirby E, Gibson AF *et al. Qual Health Res*. 2017:1049732317721478. doi: 10.1177/1049732317721478..

Accurate ID Diagnosis: The Keystone to Optimal Antimicrobial Use





[1]Filice GA *et al. Infect Control Hosp Epidemiol.* 2015 Aug;36(8):949-956. doi: 10.1017/ice.2015.113.
[2]Berner ES & Graber ML. *Am J Med.* 2008 May;121(5 Suppl):S2-23. doi: 10.1016/j.amjmed.2008.01.001.
[3]Livorsi D *et al. Infect Control Hosp Epidemiol.* 2015 Sep;36(9):1065-72. doi: 10.1017/ice.2015.136

Beware Cognitive Biases

From Mindless to Mindful Practice — Cognitive Bias and Clinical Decision Making

Pat Croskerry, M.D., Ph.D. N ENGL J MED 368;26 NEJM.ORG JUNE 27, 2013

- Anchoring: focus on one data point & ignore others
- Premature closure: not reassessing initial assessment
- Search satisfaction: stopping at one answer/ abnormality

The Usual Suspects: Normal CXR or Aspiration Pneumonia

- IDSA Guidelines require evidence of new or worsening infiltrate to make Dx (in addition to symptoms)[1]
  - Occasionally not present on admission but develops with rehydration
  - Often benefits from 72hr re-evaluation to see if alternative explanation has been identified
    - i.e. 1/3 of patients with CHF exacerbation receive antimicrobials but only ~10% have CAP[2]
- "All pneumonia comes from aspiration but not all aspiration causes pneumonia"
  - ~25% of patients who aspirate will develop pneumonia within a week[3]
    - Pre-emptive antimicrobial therapy has not been shown to prevent this
  - Aspiration pneumonitis looks very bad (CXR white out, significant fever & WBC, abrupt desat)
    - Also often improves quickly within 48hrs without antimicrobials (supportive care)

[1]Mandell LA, Wunderink RG, Anzueto A *et al. Clin Infect Dis.* 2007;44:S27.
[2]Gupta A, Mody P, Pandey A. *JAMA Intern Med.* 2015. doi:10.1001/jamainternmed.2015.5047.
[3]Joundt RA, Wong BM, Leis JA. *JAMA Intern Med.* 2015. doi:10.1001/jamainternmed.2014.8030.

The Usual Suspects: Wounds & Bilateral Cellulitis

- Cellulitis is often misdiagnosed, esp. when dermatology is not involved[1,2]
  - Watch out for "worsening on day 3" & subsequent change in therapy
- IDSA Guidelines for Diabetic Foot Infection[3]
  - Diagnosis should be clinical; micro is of limited value
- Bilateral cellulitis is extremely rare[4]
  - Consider alternative diagnoses
- What to do with positive MRSA swabs & SSTI?
  - Positive predictive value of nasal swab lower than negative PV[4]
  - Look at presence/ absence of purulence, response to non-MRSA Rx & severity of illness/ room for error

[1]Weng QY, Raff AB, Cohen JM *et al. JAMA Dermatol.* 2017;153(2):141.
[2]Strazzula L, Cotliar J, Fox LP *et al. J Am Acad Dermatol.* 2015;73(1):70.
[3]Lipsky BA, Berendt AR, Cornia PB *et al. Clin Infect Dis.* 2012:54(12):132.
[4]McCreary EK, Heim ME, Schulz LT *et al. J Emerg Med.* 2017 Jul 3. doi: 10.1016/j.jemermed.2017.05.007.

The Usual Suspects: Symptom-Free Pee

- Always, ALWAYS, **ALWAYS** ask what sx drove the UTI Dx
  - Required to differentiate cystitis vs. pyleo for appropriate Rx
  - Allows us to avoid Rx of ABU, which is still Rx'd in > 30%
- Microscopy is better than urinalysis but alone neither = Dx
  - Absence of pyuria strongly suggests alt. Dx even if bacteria present
- Symptoms
  - Classic: dysuria, frequency, urgency, suprapubic pain, flank pain, fever, nausea/ vomiting
  - Catheterized: in absence of localizing sx, UTI for fever/ WBC should be Dx of exclusion
  - Mental status changes/ functional decline in otherwise clinically stable patients should be monitored with hydration for 24-48hrs, while ruling out other possible causes

https://www.ammi.ca/?ID=127; accessed 29-09-2017.
Schulz L, Hoffman RJ, Pothof J *et al. J Emerg Med.* 2016;51(1):5.

At Discharge

- Share allergy information &/ or recommend skin testing if not already done
- De-escalate
  - Question whether OPAT is truly needed; >40% potentially avoidable[1] (PO option or just D/C)
  - Choose agent on panel with least collateral damage
- Define duration:

To figure out how long antibiotics need to be given, use the following rules:

1. Choose a multiple of 5 (fingers of the hand) or 7 (days of the week).
2. Is it an outpatient problem that is relatively mild? If so, choose something less than 10 days. After application of our multiples rule, this should be 5 or 7 days.
3. Is it *really* mild, so much so that antibiotics probably aren't needed at all but clinician or patient are insistent? Break the 5/7 rule and go with 3 days. Ditto uncomplicated cystitis in young women.
4. Is it a serious problem that occurs in the hospital or could end up leading to hospitalization? With the exception of community-acquired pneumonia (5 or 7 days), 10 days is the minimum.
5. Patient not doing better at the end of some course of therapy? Extend treatment, again using a multiple of 5 or 7 days.
6. Does the infection involve a bone or a heart valve? Four weeks (28 days) at least, often 6 weeks (42 days). Note that 5 weeks (35 days) is not an option — here the 5's and 7's cancel each other out, and chaos ensues.
7. The following lengths of therapy are inherently weird, and should generally be avoided: 2, 4, 6, 8, 9, 11, 12, 13 days. Also, 3.14159265 days.

[1]Spivak E, Kendall B, Orlando P *et al. Infect Control Hosp Epidemiol.* 2015;36(9):1103.
Sax, Paul. How to figure out the length of antibiotic therapy. HIV and ID Observations (Blog), NEJM Journal Watch. Posted 22-10-2010.

At Discharge: Defining Duration of Therapy[1]

- Increasing evidence to support that shorter durations > longer ones
  - BMJ Editorial this summer → clinicians not sure how to translate to patients[2]
  - In all cases, look at rate of improvement rather than risk for recurrence/ severity of presentation
- CAP: minimum of 5d, with 48hrs afebrile & clinically stable
- HAP: most episodes can be treated with 7d
- SSTI: most episodes can be treated with 5d, although a subset will need longer
- UTI: depends on location & agent, but generally no more than 7d (FQ) or 10d (BL)
  - Consider as long as 14d if difficulty obtaining source control but not always necessary
- IAI with adequate source control: 4d

[1]Valiquette L, Laupland KB. *Can J Infect Dis Med Microbiol.* 2015;26(4):174.
[2]Llewelyn MJ, Fitzpatrick JM, Darwin E *et al. BMJ.* 2017;358:j3418.

Summary

- The antibiotic apocalypse is nigh…
- Non-ID Pharmacists represent an untapped resource for stewardship
  - Many opportunities for intervention exist at common points of care, w/ or w/o formal program
- Focus on
  - Delabeling unnecessary & harmful penicillin allergies
  - Making sure there is actually an infection that requires antimicrobials
    - Part of this is promoting stewardship of culturing
  - Thinking about optimizing (de-escalation, defining duration, IV to po conversion) on discharge