Antibiotic Combinations for Hospital-acquired Pneumonia (HAP) and Ventilator-associated Pneumonia (VAP) Treatment

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TRENDS

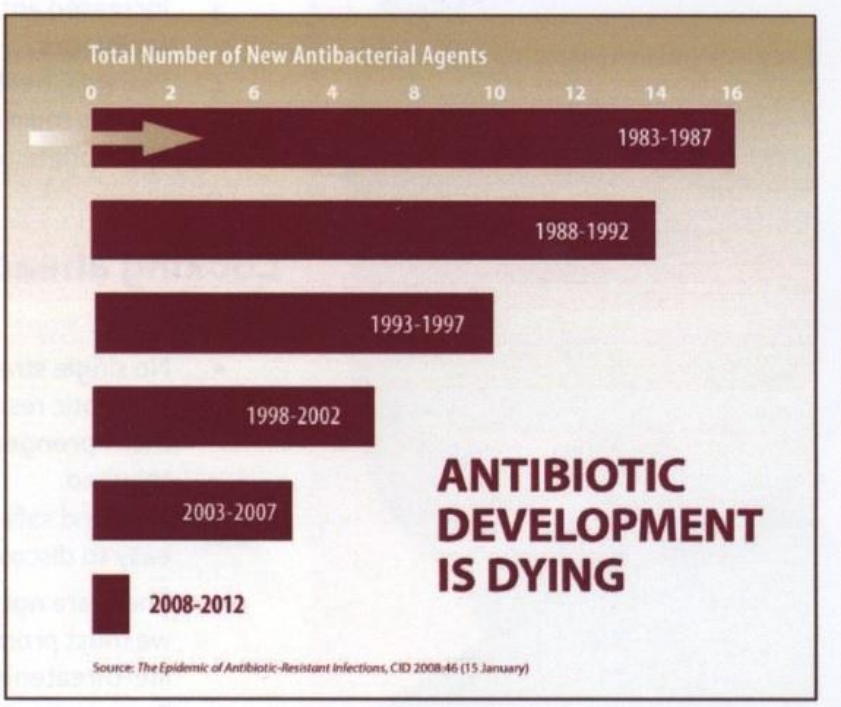
The world is getting smaller (and things are changing faster and faster)

In healthcare, now we must integrate care by locations and disciplines (outpatients / emergency dept / ICU / inpatients)

We face many of the same challenges:

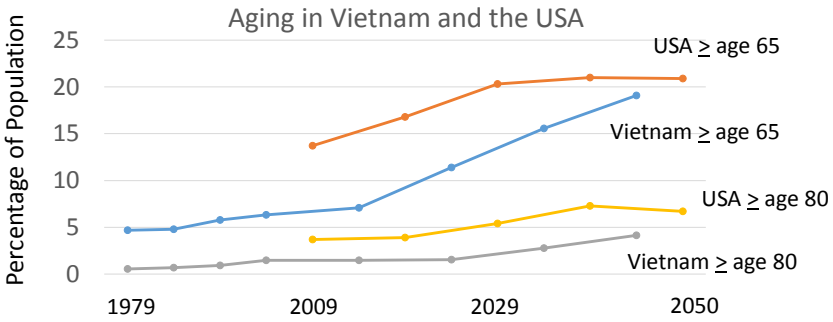
- Older and sicker population
- More antibiotic-resistant organisms,
- Too few new antibiotics
  (with high costs and only i.v. form)

But there are differences . . .


Total Number of New Antibacterial Agents
0
2
6
4
8
10
12
14
16
1983-1987
1988-1992
1993-1997
1998-2002
2003-2007
2008-2012
ANTIBIOTIC DEVELOPMENT IS DYING
Source: The Epidemic of Antibiotic-Resistant Infections, CID 2008:46 (15 January)

CHANGING PATIENT POPULATIONS

Population growing; percentage of elderly increasing
More chronic diseases (heart, lung, kidney)
More immunocompromised (cancer, HIV, transplant)
Nursing facilities with the elderly and chronically ill



Spectrum of lower respiratory tract infections

Bronchitis / COPD exacerbation; may be noninfectious

Mild – moderate "walking pneumonia" treated in outpatient setting with oral antibiotics – may be viral, mycoplasmal, etc.

Mild to moderate community-acquired pneumonia requiring brief hospital stay, rapid discharge – often pneumococcal (but may be drug-resistant)

Severe community-acquired pneumonia due to many causes: pneumococcal, overwhelming influenza, viral with superinfection or organ failure, community-acquired MRSA, GNR (in susceptible patients, notably COPD)

Spectrum of lower resp tract infections (2)

Healthcare-associated pneumonia (HCAP) is related to:

- i.v. Rx, wound care, i.v. chemoRx within past 30 days
- Residence in nursing home, long-term care facility
- Acute care hospitalization $\geq$ 2 days within past 90 d
- Attendance at hospital or hemodialysis clinic $\leq$ 30 d

Hospital-acquired pneumonia (HAP)(prob overdiagnosed)

develops $\geq$ 48h after admission and "not incubating" on admission

Ventilator-associated pneumonia (VAP) develops more than 48-72h after endotracheal intubation

Niederman MS, Craven DS, et al. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171: 388-416.

BACTERIAL ANTIBIOTIC RESISTANCE

Enzymes to destroy antibiotics:

- beta-lactamases (incl. ESBL's, carbapenemases)
  - common in E-coli, Klebsiella, other GNR's
  - transmissible by plasmids

Change in antibiotic target:

- Altered penicillin-binding proteins (PBP's)
  - seen in *Strep pneumoniae, Staph aureus*
- Altered DNA gyrase (fluoroquinolone target)

Barriers to antibiotic penetration:

- Altered porin proteins (for membrane transport)
  - a mechanism of resistance in Pseudomonas

Bacteria may have multiple resistance factors

Challenges in managing the critically ill pneumonia patient

Severe CAP and HCAP often seen first in ED

HAP estimated at 5 to 10 per 1,000 hospital admissions and 25% of all ICU infections

Major risk factors for HAP are age > 70 yrs, chronic lung diseases, depressed consciousness, aspiration and many others

Incidence of pneumonia 6 to 20-fold higher in ventilated patients and occurs in 9 to 27% of intubated patients

Niederman MS, Craven DS, et al. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171: 388-416.

BACTERIAL COLONIZATION VS. INFECTION

Sometimes a difficult problem:

- Sputum colonization with gram-positive and gram-negative bacteria and fungi common in COPD, the chronically ill, and intubated patients
- Accurate sputum gram stain and cuture information (Deep suctioned sputum ideal)
  (? Quantitative counts) very helpful
- Radiography changes (CXR, CT scanning) important
- Clinically situation (fever, worsening sputum and hypoxia, and overall condition) most critical
- Bronchoscopy may be necessary (for diagnosis and sometimes therapy)

Sepsis & Prognostic Factors for HAP & VAP

Awareness of possible sepsis is critical

- monitor temperature, BP, lactate levels

Use of biomarkers to predict short-term CAP mortality (in order of value): proadrenomedullin > prohormone form atrial natriuretic peptide > cortisol > procalcitonin > copeptin +/- C-reactive protein

Viasus D, et al, Biomarkers for predicting short-term mortality in community-acquired pneumonia: A systemic review and meta-analysis. J Infect 2016: 72: 273-82.

Procalcitonin predictive of increased mortality from CAP or VAP (odds ratio aroud 4.18 to 4.38) but need to use assay with low cut-off (0.a5 ng/ml)

Liu D, et al, Prognostic value of procalcitonin in pneumonia: A system review and meta-analysis. Respirology 2016: 21: 280-88.

? use procalcitonin to decide when antibiotics can be stopped in HAP

Antimicrobial Resistance in RTI Pathogens

Resistant microorganisms in USA and around the world

- Penicillin-resistant *Streptococcus pneumoniae*
- *Staphylococcus aureus* and MRSA
- Enteric Gram-negative Rods (GNR's) , especially ESBL-positive
- Non-lactose fermenting (NLF) GNR's such as Pseudomonas versus Acinetobacter, spp. Stenotrophomonas m., Burkholderia c.
- Fungi usually colonizers except in immunocompromised

Risks for HCAP with resistant organisms:

- Recent hospital stay > 48h during past 90 days = 4 points
- Residence in a nursing home = 3 points
- Chronic hemodialysis = 2 points
- Critical illness = 1 point
- MDR-organism pt's averaged 4, No MDR-organism averaged 1

Centers for Disease Control and Prevention Vital Signs: Preventing antibiotic-resistant infections in hospitals – United States, 2014. MMWR 65; 2016: accessed on line, 3-5-16)

Shore AF, et al. Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. Clin Infect Dis 2012; 54: 19


NICU
STOP
AUTHORIZED PERSONNEL ONLY
TRU-D
SMARTUVC ROOM DISINFECTION
TRU-D SMARTUVC


DANGER
DO NOT ENTER
NOTICE
KEEP THIS DOOR CLOSED
CAUTION
ULTRAVIOLET LIGHT
CUIDADO
LUZ ULTRAVIOLETA
DANGER
DO NOT ENTER
NOTICE
KEEP THIS DOOR CLOSED
CAUTION
ULTRAVIOLET LIGHT
CUIDADO
LUZ ULTRAVIOLETA

A8 | THE PHILADELPHIA INQUIRER | WEDNESDAY, MARCH 20, 2013

Kathleen Dunn stands outside a Doylestown room as the UV system works.
TOM GRALISH / Staff Photographer

The Xenex system at work. Because of risk to people, the camera was left inside.

New weaponry for hospitals

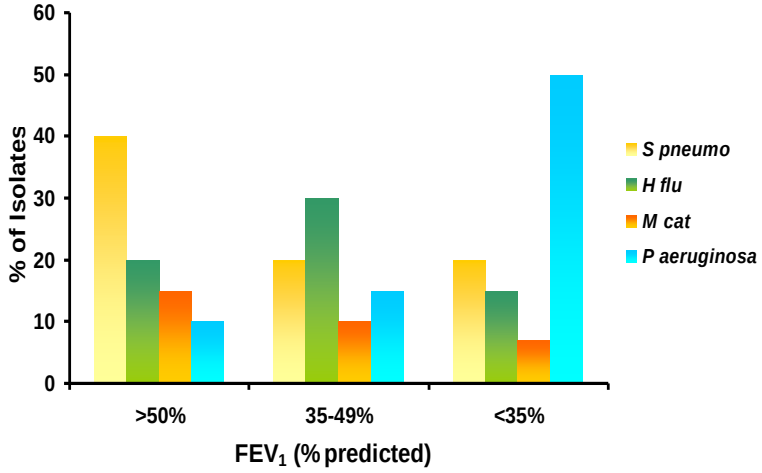
One system zaps a room with ultraviolet light, killing deadly germs.

PNEUMONIA IN COPD PATIENTS

Always a concern:

- Acute Exacerbation of COPD (AECOPD) common, <u>may</u> be associated with bacterial infection
- Range of pathogens range from *Strep pneumoniae, Haemophilus i., Moraxella to Pseudomonas, Acinetobacter, Klebsiella* (especially in Asia)
- Risk of *Pseudomonas* rises with decreasing FEV1
- Treatment of <u>true</u> pneumonia in COPD usually follows HCAP guidelines
- Clinical judgment and close followup are critical

Bacteria in AECOPD



Baughman et al. *Semin Resp CCM*; 21: 87-96.

Resistant Organisms in HAP & VAP

HAP, VAP epidemiology DIFFERENT from CAP; HCAP VARIABLE

HAP epidemiology:

- MSSA 13%, MRSA 20%, *Pseudomonas a*. 9%, *Acinetobacter spp*. 3%, *Stenotrophomonas m.* 1%

VAP epidemiology:

- MSSA 9%, MRSA 18%, *Pseudomonas* 18%, *Acineto-bacter* spp. 8%, *Stenotrophomonas m.* 7% other 9%

Weber DJ, et al. Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia Infect Control Hosp Epidmiol 2007; 28: 825.

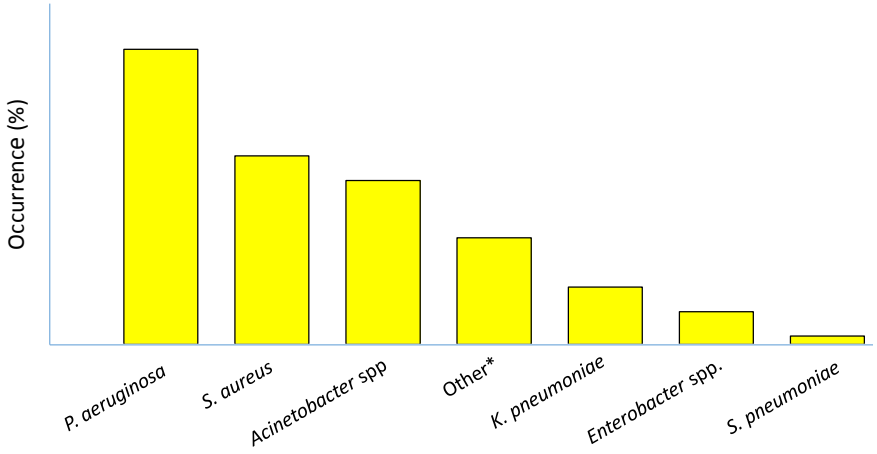
Pathogens vary according to location!

Recent British study suggested most common VAP flora:

- *Pseudomonas* (30.1%), Enteric GNR's (35.7% including *E. coli, Klebsiella, Enterobacter c.),* and MRSA 10.8%

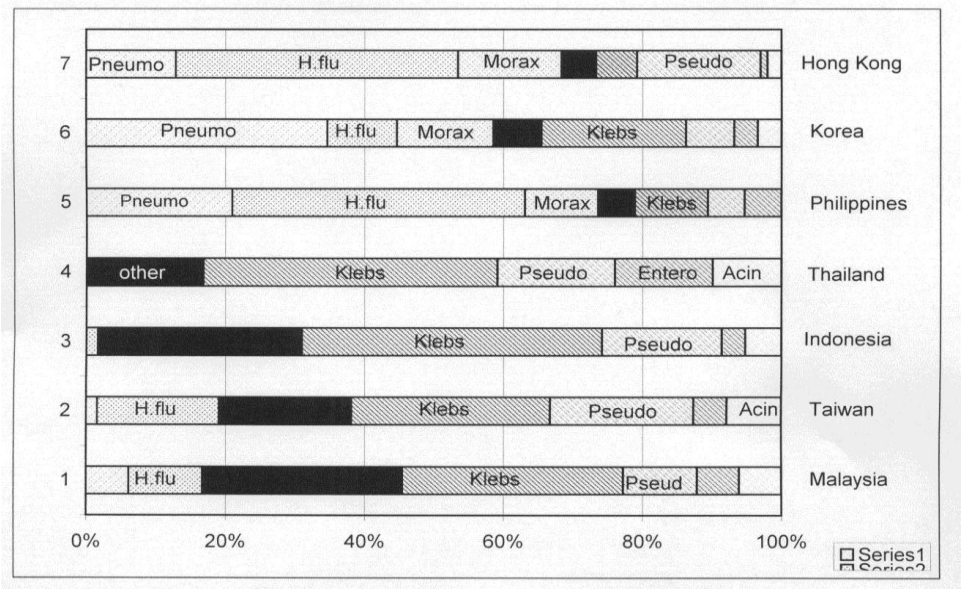
Browne E, et al. A national survey of the diagnosis and management of suspected ventilator-associated pneumonia. BMJ Open Resp Res 2014: 1; 1-7

Pathogens Associated With Inadequate Therapy in HAP



*Other: *H. influenzae, E. coli, P. mirabilis, S. marcescens, Legionella* spp.

Adapted from Kollef MH. *Clin Infect Dis*. 2000;31:S131-S138



Hui, D.S., Ip, M, Ling, T., . . . Liu, H.H. A Multicentre Surveillance Study on the Characteristics, Bacterial Aetiologies and in vitro Antibiotic Susceptibilities in Patients with Acute Exacerbations of Chronic Bronchitis. Respirology 2011; 16: 532-9 (2011)

Diagnostic Studies in HAP & VAP

Sputum gram stain may not be available, be contaminated

Sputum culture and susceptibility testing take time; can be affected by prior antibiotic therapy

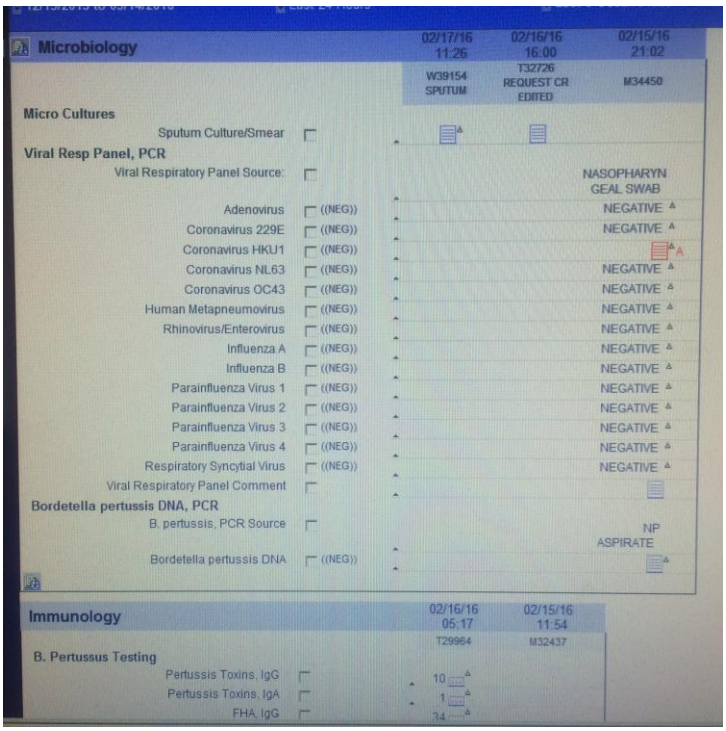
Influenza A&B Ag studies are useful during epidemics

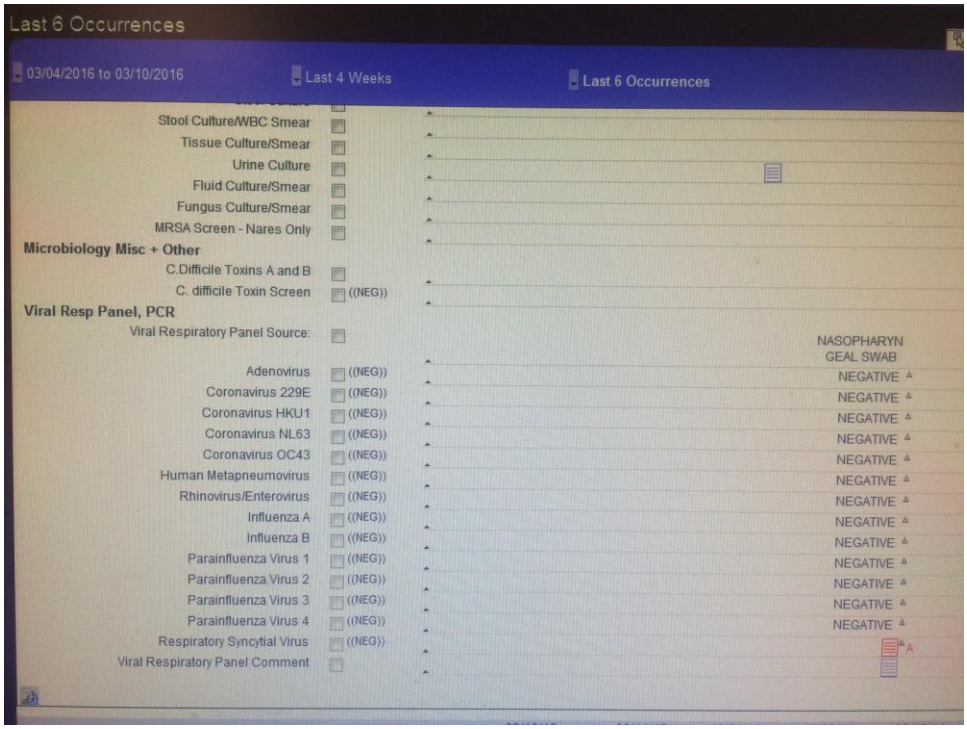
New developments in viral diagnosis:

- nasal aspirate → viral respiratory panel (incl. coronavirus, RSV, rhinovirus/enterovirus, human metapneumonia virus
- may allow treatment with specific antiviral and/or discontinuation of antibacterial therapy
- relatively quick but also expensive (US $138)

Streptococcus pneumonia Ag, Legionella urine Ag variable

Mycoplasma IgM takes time; PCR Antigen tests quicker





Antibiotic Selection for HAP & VAP

Antibiotic selection usually empiric, based on local epidemiology, clinical situation

IDSA /ATS guidelines for HAP & VAP from 2005, to be revised soon

- MRSA: vanco (in higher doses with trough 15-20 ug/ml), ? ceftaroline, linezolid > TMP-SMX, clinda, doxy and not daptomycin (inactivated by pulmonary surfactant)
- GNR's: beta-lactams (esp. 3rd gen ceph), beta-lactam/inhibitor combinations (e.g. pip/tazo, carbapenems (e.g., imipenem, meropenem, doripenem and ertapenem, aminoglycosides (gent, tobra, amikacin), newer GNR agents: Ceftazidime-avibactam (Avycaz®) for ESBL-GNR OR ceftolozane/tazobactam (Xerbaxa®) vs pseudomonas
- Tigecycline cure rates in HAP less than with imipenem (tigecyclie 68%, imipenem = 78%)

  Freire AT, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis 2010; 68: 140

Aerosolized aminoglycoside (tobramycin, using specific nebulizer)

Fluoroquinolones offer another antibiotic class, poss. oral therapy

Fluoroquinolones in HAP & VAP

Offer monotherapy (potentially oral) in CAP; cover atypical resp pathogens *(Mycoplasma, Legionella, Chlamydophila)*

Blazquez RM, et al. Antimicrobial chemotherapy for Legionnaires Diseases: Levofloxacin vs. macrolides. Clin Infect Dis 2005; 40: 800-6

Levofloxacin original "respiratory fluoroquinolone;" levofloxacin and ciprofloxacin used in HAP/VAP; moxifloxacin = less GNR activity; resistance is noted in GNR's incl. *Pseudomonas* up to 20-30%

Maximum dosing is levoflox 750mg i.v. q24h, cipro 400 mg i.v q8h

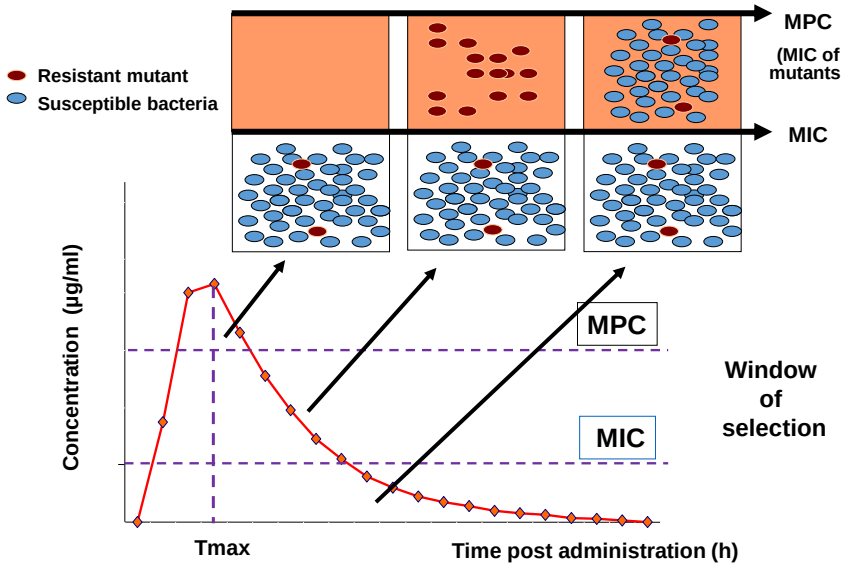
QTc prolongation and drug interactions are serious concerns

Levofloxacin has excellent safety profile, safer re QTc prolongation, hypoglycemia, skin rashes comp with other fluoroquinolones; pharmacokinetics not changed in critically ill

Roberts JA, et al. Does critical illness change levofloxacin pharmacokinetics? Antimicrob Agents Chemother 2015 (E-published 14 December 2015)

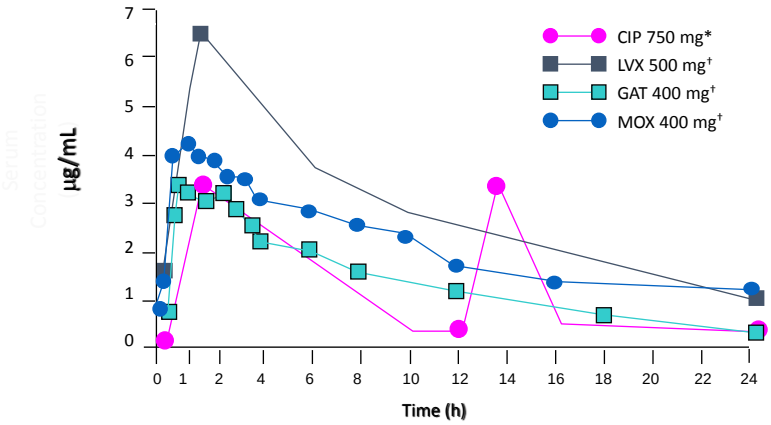
What is the role of combination Rx (double, triple Rx, combining different classes) and how good is evidence

Window of selection & mutant prevention concentration



Baquero F & Negri MC. *BioEssays* 1997;19:731–6.
Drlica K. *ASM News* 2001;67:27–33.

Fluoroquinolone Serum Concentrations vs Time After Oral Administration



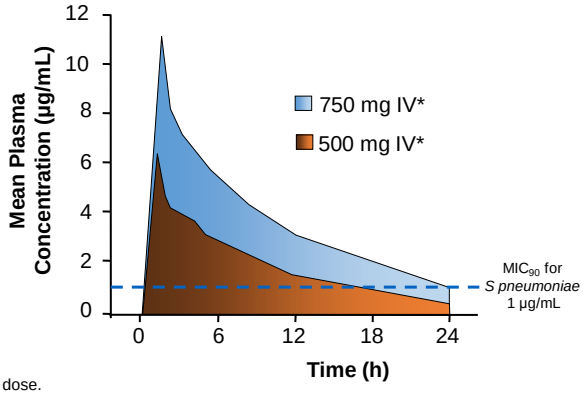
CIP = ciprofloxacin, LVX = levofloxacin, GAT = gatifloxacin, MOX = moxifloxacin. * 2 doses; †Single dose.
Data from Tequin™ PI; Lettieri et al, 1992; Child et al, 1995; Avelox™ PI.

750-mg Regimen Provides Optimized Pharmacokinetic Parameters

- 750-mg dose provides:
  - Higher plasma concentrations vs 500-mg dose
  - 1.9-fold increase in C_{max}
  - 2.3-fold increase in $AUC_{0\text{-}24}$

Peak Plasma Levels

Mean Levofloxacin Plasma Concentration: Time Profiles



*In healthy volunteers who received a single dose.

LEVAQUIN® (levofloxacin) Prescribing Information. Raritan, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Levofloxacin Advantages

Levofloxacin has advantages in the treatment of pneumonias:

- broad gram-positive and gram-negative coverage
- convenient daily dosing
- few true allergies, generally good tolerability

Certain attributes are helpful in treating HAP and VAP:

- excellent levels in blood and penetration to lung tissue
- potential for streamlining to oral or feeding tube route

Antibiotic combinations with different mechanisms of action are advocated for synergy / resistance prevention (esp. pseudomonas)

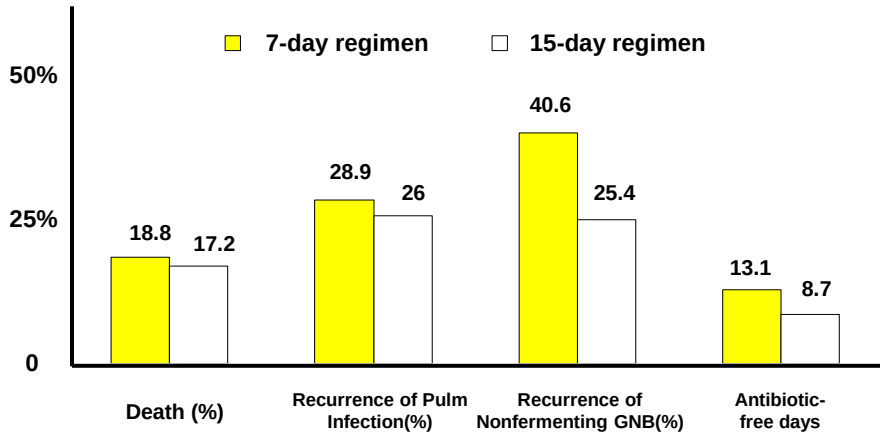
- a combination of levofloxacin with imipenem shows more complete killing of pseudomonas compared with either alone

  Uoyama S. et al. Jpn J Antimicrib 2012; 65-355-63

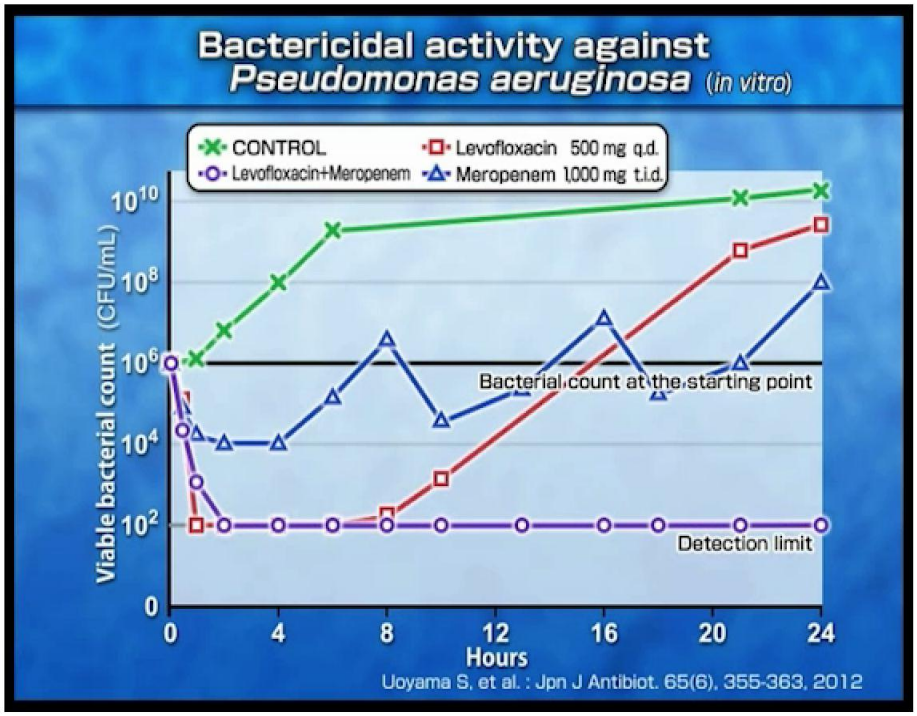
7-8 days of antibiotics adequate for pneumonia in the ICU, except pseudomonas and related GNR's (= 14-15 days)

Barrett J, Edgeworth J, Wyncoll D. Shortening the course of antibiotic treatment in the intensive care unit. Expert Rev of Anti-Infective Therapy (online 3 Feb 2015; 463-71)

8 vs. 15 Days of Antibiotic Therapy Ventilator-Associated Pneumonia



Chastre J, et al. *JAMA*. 2003;290:2588-2598



COMBINATION VS. MONOTHERAPY

Ultimately a clinical judgement:

In Community-acquired Pneumonia (CAP), either combination therapy (macrolide + beta-lactam) or fluoroquinolone is effective

For Healthcare-associated Pneumonia (HCAP) and Hospital-acquired Pneumonia (HAP) in mild to moderately ill patients, monotherapy (beta-lactam or fluoroquinolone is still reasonable

For moderately to severely ill patients with HAP and most VAP patients, combination therapy is preferred (at least initially due to risk of MDR)

MRSA risk must be judged separately

LEVOFLOXACIN 750 mg versus 500 mg twice-a-day

Levofloxacin is a safe drug (vis-à-vis other FQ, classes)

750 mg dose has advantages in PK/PK over 500 mg:

- Penetration, serum and tissue levels, rapidity and degree of bacterial killing

Extensive research supports 750 mg daily dose and short course therapy

1000 mg total daily dose unnecessary:

- Even in USA patients (weight > 100 or even 150 kg) 750 mg dose effective
- Higher dose increases antibiotic exposure / cost

SUMMARY & RECOMMENDATIONS

Always expect the unexpected:

(bird flu, SARS, MERS, Ebola, dengue, chikungunya, Zika, multidrug-resistant pathogens)

Remember prevention (manage COPD, CHF, aspiration)

Early diagnosis of sepsis and treatment of pneumonia

Monitoring (lactate, BP, etc.)

Know local populations, common pathogens, resistance

Choice of antibiotics and for minimum length of Rx

Prevent spread of infection, antibiotic resistance

Anticipate coming needs

Thank You!