

# Why do we need to reconsider standard dosing regimens

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# Early days of antibiotics

- **1940s:** Penicillin 100,000 to 120,000 units/day iv
- **Today:** 5-24 million units/day iv

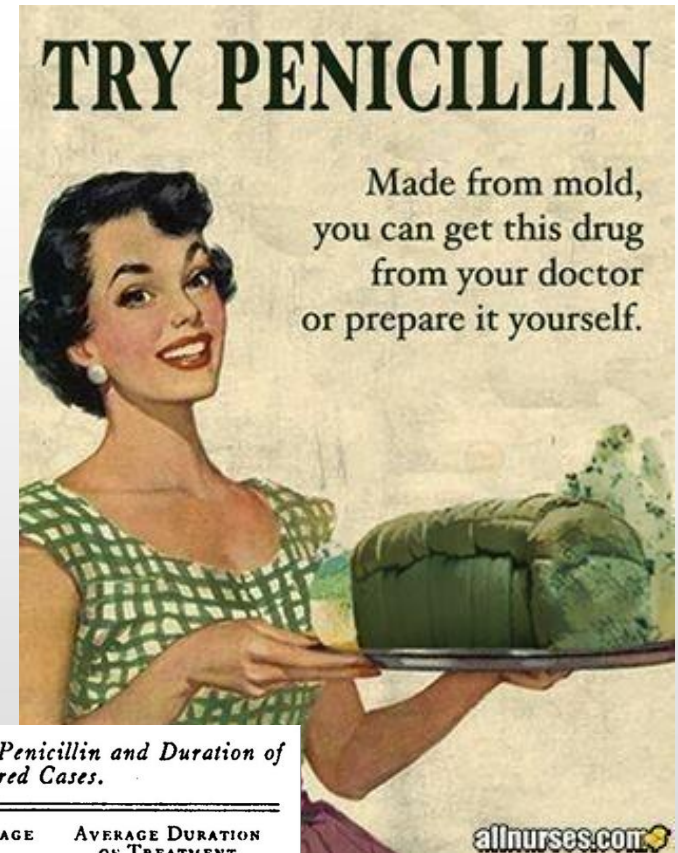


TABLE 2. Average Total Dosage of Penicillin and Duration of Treatment in Recovered Cases.

TYPE OF CASE	AVERAGE TOTAL DOSAGE OF PENICILLIN units	AVERAGE DURATION OF TREATMENT hr.
Group I	411,000	86
Group II	728,000	162
Severity:		
Grade 2	317,000	66
Grade 3	477,000	107
Grade 4	735,000	148
All cases	507,000	107

N Engl J Med 1945; 232:747-755

# Early days of antibiotics

- Amoxicillin, adult dosing
  - 1980s: 3x 250mg/day oral
  - Now: 3x 500-875
- Amoxicillin, paediatric dosing
  - 1980s: 37.5-75 mg/kg divided three times per day
  - Now: 90 mg/kg/day divided two times per day

# Old antibiotics

- Europe: National agencies
- EMA since 1995
- Article 30: **Harmonisation**
- Article 31: **Public health interest** (Quality, safety, efficacy)
  - Examples: Fluoroquinolones, polymyxins (New SPC valid since 12/2014)
- Article 5(3): Scientific issues
  - Example polymyxins: Revision of the Ph. Eur. Monograph

# Dosage creep

- Daptomycin
  - Clinical trials 2mg/kg
  - FDA approved in 2003: 4 mg/kg once daily for the treatment of complicated SSSI caused by specific gram-positive bacteria
  - Post-approval studies: 6 mg/kg
  - Label extension: 4 mg/kg for skin infections and 6 mg/kg for bacteraemia or right-sided endocarditis.
  - Today:  $\geq 10$  mg/kg recommended for endocarditis or bacteraemia including those associated with intravascular catheter and implant-related infections

# Current additional considerations for dosing regimens

- Special patient populations
  - Obese patients
  - Critically ill patients
- Duration of treatment
- Extra-, intracellular infections, tissue infections

# Future dosing challenges

- Non-traditional approaches
  - Non-MIC drugs
  - Complex delivery systems
  - Phages
  - Microbiome-modulating drugs
  - Immunomodulating
  - Nanoparticles
- Traditional approaches
  - Small therapeutic window
  - Emergence of resistance
  - Potentiators