Short Course IV and Early IV-to-Oral Antibiotic Treatment

Infectious Disease Forum: Update of the Sixth Edition of Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy (IMPACT)

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Misbelief:

1. IV route is more effective
2. IV route has better tissue penetration
3. The broader the better
4. The longer the safer

Inappropriate route of administration of antimicrobials
Inappropriate choice of antimicrobials
Longer-than-necessary duration

Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Therapeutic Advances in Drug Safety. 2014;5(6):229-241.

Antimicrobial Resistance (AMR)

A global disease burden study has estimated that in 2021 there were 4.71 million deaths associated with bacterial AMR, including 1.14 million deaths attributable to bacterial AMR.

Forecasts show that an estimated 1.91 million deaths attributable to AMR and 8.22 million deaths associated with AMR could occur globally in 2050.

The World Bank estimates that AMR could result in US$ 1 trillion additional healthcare costs by 2050, and US$ 1 trillion to US$ 3.4 trillion gross domestic product (GDP) losses per year by 2030.

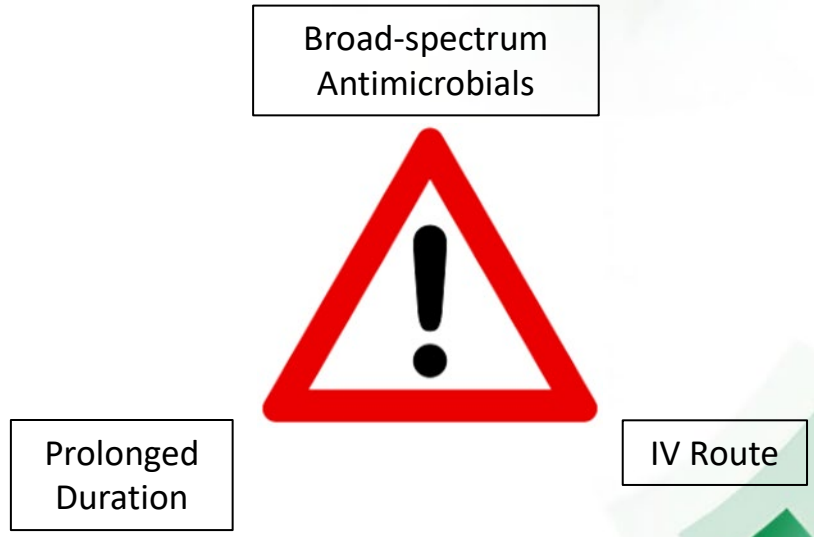
GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. *The Lancet*. 2024;404(10459):1199-1226. doi:10.1016/S0140-6736(24)01867-1

Jonas OB, Irwin A, Berthe FCJ, Le Gall FG, Marquez PV. *Drug-resistant infections: a threat to our economic future*. Vol 2. World Bank Group; 2017. https://documents.worldbank.org/en/publication/documents-reports /documentdetail/323311493396993758/final-report

Institutional level

Harm:

- Cost
  - IV Levofloxacin ($20.2/day)
  - PO Levofloxacin ($1.21/day)
- Hospital occupancy
- Nursing time / manpower:
  - Oral: 2.42 min
  - IV Bolus: 5.53 min
  - IV infusion: 10.27 min
- Environmental impact

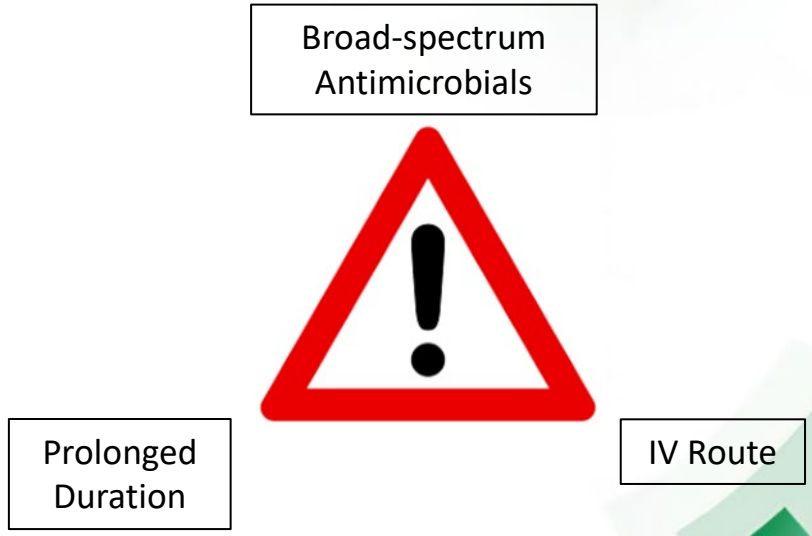


Michelle Tan, Neil Powell, Daniel Hearsey, P35 Impact of IV to oral antibiotic switch optimization on nurse time and plastic waste at the Royal Cornwall Hospital Trust, *JAC-Antimicrobial Resistance*, Volume 6, Issue Supplement_2, August 2024, dlae136.039

Individual Level

Harm:

- AMR
- Phlebitis
- Disruption of microbiome
- *Clostrioides difficile* infection
- Increasing risk of secondary infections
- Hospital-acquired Infection
- Restraint / Immobilization
- Prolonged hospitalization
- Financial Cost
- Adverse drug reactions from antimicrobials



……. and not exhaustive

Li HK, Agweyu A, English M, Bejon P. An unsupported preference for intravenous antibiotics. PLoS Med 2015;12:e1001825.

Nathwani D, Lawson W, Dryden M, Stephens J, Corman S, Solem C, et al. Implementing criteria-based early switch/early discharge programmes: a European perspective. Clin Microbiol Infect 2015;21:S47e55.

What could offer help ?

- International and Local Guidelines
- Evidence-based Medicine
  - Randomized Controlled Trials (RCTs)
  - Meta-analysis / Systematic Review
- Pharmacological Studies

Misbelief:

1. IV route more effective
2. IV route has better tissue penetration
3. The broader the better
4. The longer the safer

Yek, C., Lawandi, A., Evans, S. R., & Kadri, S. S. (2023). Which trial do we need? Optimal antibiotic duration for patients with sepsis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 29(10), 1232–1236.

Shorter Course of Antibiotics

Best Practice Advice 1: *Clinicians should limit antibiotic treatment duration to 5 days when managing patients with COPD exacerbations and acute uncomplicated bronchitis who have clinical signs of a bacterial infection (presence of increased sputum purulence in addition to increased dyspnea, and/or increased sputum volume).*

Best Practice Advice 2: *Clinicians should prescribe antibiotics for community-acquired pneumonia for a minimum of 5 days. Extension of therapy after 5 days of antibiotics should be guided by validated measures of clinical stability, which include resolution of vital sign abnormalities, ability to eat, and normal mentation.*

Best Practice Advice 3: *In women with uncomplicated bacterial cystitis, clinicians should prescribe short-course antibiotics with either nitrofurantoin for 5 days, trimethoprim–sulfamethoxazole (TMP–SMZ) for 3 days, or fosfomycin as a single dose. In men and women with uncomplicated pyelonephritis, clinicians should prescribe short-course therapy either with fluoroquinolones (5 to 7 days) or TMP–SMZ (14 days) based on antibiotic susceptibility.*

Best Practice Advice 4: *In patients with nonpurulent cellulitis, clinicians should use a 5- to 6-day course of antibiotics active against streptococci, particularly for patients able to self-monitor and who have close follow-up with primary care.*

7 is no longer a magic number

Lee, R. A., Centor, R. M., Humphrey, L. L., Jokela, J. A., Andrews, R., Qaseem, A., Scientific Medical Policy Committee of the American College of Physicians, Akl, E. A., Bledsoe, T. A., Forciea, M. A., Haeme, R., Kansagara, D. L., Marcucci, M., Miller, M. C., & Obley, A. J. (2021). Appropriate Use of Short-Course Antibiotics in Common Infections: Best Practice Advice From the American College of Physicians. Annals of internal medicine, 174(6), 822–827.

Shorter Course of Antibiotics

Diagnosis	Short (d)	Long (d)	Result	No. of RCTs
Community-acquired pneumonia	3–5	5–14	Equal	14
Atypical community-acquired pneumonia	1	3	Equal	1
Possible pneumonia in ICU	3	14–21	Equal	1
Ventilator-associated pneumonia	8	15	Equal	2
Complicated UTI/pyelonephritis	5 or 7	10 or 14	Equal	9
Complicated intra-abdominal infection	4–8	10–15	Equal	2
Gram-negative bacillus bacteremia	7	14	Equal	3
Cellulitis/wound/abscess	5–6	10	Equal	4
Osteomyelitis	42	84	Equal	2
Osteomyelitis s/*P* implant removal	28	42	Equal	1
Diabetic osteomyelitis s/*P* Debridement	10–21	42–90	Equal	2
Septic arthritis	14	28	Equal	1
Acute exacerbations of bronchitis and sinusitis	≤5	≥7	Equal	>25
Neutropenic fever	AFx72 h/3d	ANC > 500/9d	Equal	2
Perioperative prophylaxis	0–1	1–5	Equal	56
Plasmodium vivax malaria	7	14	Equal	1
Erythema migrans (Lyme disease)	7	14	Equal	1

Abbreviations: ANC, absolute neutrophil count; d, day; h, hour; ICU, intensive care unit; RCT, randomized controlled trial; Refs., references; UTI, urinary tract infection.

Davar, K., Clark, D., Centor, R. M., Dominguez, F., Ghanem, B., Lee, R., Lee, T. C., McDonald, E. G., Phillips, M. C., Sendi, P., & Spellberg, B. (2022). Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV. *Open forum infectious diseases*, *10*(1), ofac706.

Shorter Course of IV Antibiotics

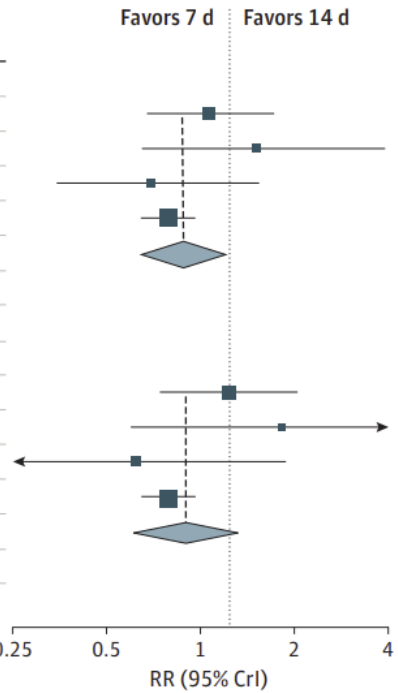
JAMA Network Open

Original Investigation | Infectious Diseases

Seven vs Fourteen Days of Antibiotics for Gram-Negative Bloodstream Infection
A Systematic Review and Noninferiority Meta-Analysis

Todd C. Lee, MD, MPH; Connor J. Prosty, MD; Michael Fralick, MD, PhD; Angela Huttner, MD; Emily G. McDonald, MD, MSc; José Molina, MD, PhD; Mical Paul, MD; Ruxandra Pinto, PhD; Asgar Rishu, MBBS, MHSc; Elodie von Dach, PhD; Dafna Yahav, MD; Rob Fowler, MDCM; Nick Daneman, MD, MSc

Source	Deaths/total No. of patients: 7 d of Therapy	14 d of Therapy	RR (95% CrI)
Intention to treat			
Yahav et al,[4] 2019	36/306	32/298	1.10 (0.70-1.72)
von Dach et al,[5] 2020	14/169	9/165	1.52 (0.68-3.41)
Molina et al,[3] 2022	10/117	15/127	0.72 (0.34-1.55)
BALANCE Investigators,[7] 2024	166/1292	197/1255	0.82 (0.68-0.99)
Bayesian	226/1884	253/1845	0.91 (0.69-1.22)
τ=0.13 (95% CrI, 0.02-0.33)			
Probability of noninferiority, 97.8%			
Per protocol			
Yahav et al,[4] 2019	33/280	26/276	1.25 (0.77-2.03)
von Dach et al,[5] 2020	9/141	5/143	1.83 (0.63-5.31)
Molina et al,[3] 2022	5/92	9/108	0.65 (0.23-1.88)
BALANCE Investigators,[7] 2024	120/1014	159/1072	0.82 (0.68-0.99)
Bayesian	167/1527	199/1599	0.93 (0.68-1.32)
τ=0.15 (95% CrI, 0.02-0.38)			
Probability of noninferiority, 95.1%			



Lee, T. C., Prosty, C. J., Fralick, M., Huttner, A., McDonald, E. G., Molina, J., Paul, M., Pinto, R., Rishu, A., von Dach, E., Yahav, D., Fowler, R., & Daneman, N. (2025). Seven vs Fourteen Days of Antibiotics for Gram-Negative Bloodstream Infection: A Systematic Review and Noninferiority Meta-Analysis. JAMA network open, 8(3), e251421.

Shorter Course of IV Antibiotics

Short versus prolonged duration of therapy for *Pseudomonas aeruginosa* bacteraemia: a systematic review and meta-analysis

N. Ranganath [a,*], L.C. Hassett [b], O.M.A. Saleh [a], Z.A. Yetmar [a,c]

14 is no longer a magic number

analyzing 6 retrospective cohort studies totally 1746 patients

6-11 days vs 12-21 days

demonstrates similar rates of 30-day all-cause mortality and recurrent infection

Ranganath, N., Hassett, L. C., Saleh, O. M. A., & Yetmar, Z. A. (2024). Short versus prolonged duration of therapy for Pseudomonas aeruginosa bacteraemia: a systematic review and meta-analysis. The Journal of hospital infection, 148, 155–166.

Shorter Course of IV Antibiotics

Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review

Noah Wald-Dickler, MD,[a,b,c] Paul D. Holtom, MD,[a,b] Matthew C. Phillips, MD,[a] Robert M. Center, MD,[d,e] Rachael. A. Lee, MD,[d,e] Rachel Baden, MD,[a] Brad Spellberg, MD[a]

Diagnosis	No. of RCTs Demonstrating IV > Oral	No. of RCTs Demonstrating Oral ≥ IV
Osteomyelitis	0	9 (all equal)
Bacteremia	0	10 (8 equal, 2 superior cure for oral)
Endocarditis	0	3 (2 equal, 1 superior mortality for oral)

Abbreviations: IV, intravenous; RCT, randomized controlled trial.

Early IV-to-Oral Switch !

Wald-Dickler, N., Holtom, P. D., Phillips, M. C., Center, R. M., Lee, R. A., Baden, R., & Spellberg, B. (2022). Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review. The American journal of medicine, 135(3), 369–379.e1.

Early IV-to-oral switch

Antimicrobial	Oral bioavailability (%)
Linezolid	~100%
Levofloxacin	~100%
Tedizolid	92%
Cefalexin	90–100%
Clindamycin	75–90%
Fluconazole	>90%
Moxifloxacin	86%
Metronidazole	80 to >95%
Amoxicillin	74–92%
Ciprofloxacin	65–85%
Sulfamethoxazole-trimethoprim	70 to >95%
Doxycycline and tetracycline	>90% with food

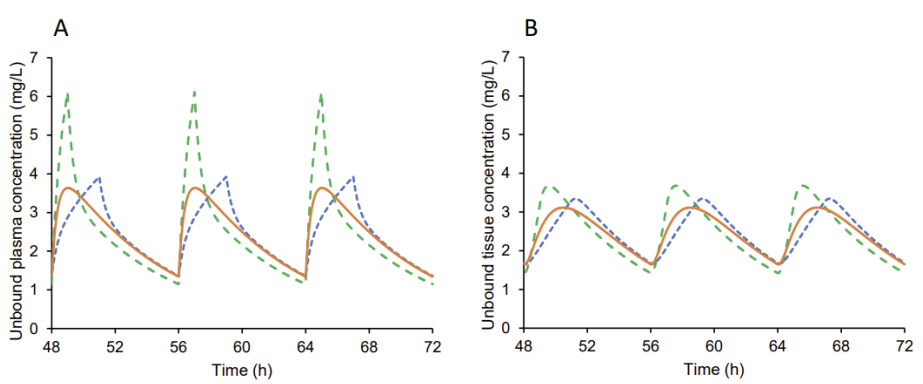


Fig. 1. Simulated unbound concentration-time profiles at steady state in plasma (A) and tissue (interstitial fluid) (B) following 8-hourly antibiotic dosing as 1-h infusions (green long dashed line), 3-h infusions (blue short dashed line) and oral dosing (orange solid line). The same antibiotic dose was simulated for all regimens, elimination was linear, and the oral bioavailability was 100%. The hypothetical antibiotic has a kinetically distinct peripheral (tissue) compartment, as occurs with most antibiotics, and the unbound concentrations in tissue (interstitial fluid) are proportional to the concentrations in the peripheral compartment. The simulated pharmacokinetic characteristics are similar to clinically used antibiotics. Steady state was simulated to represent scenarios where intravenous regimens that were initiated at zero time were either continued (green and blue lines) or switched to an oral regimen (orange line) at 48 h.

Landersdorfer, C. B., Gwee, A., & Nation, R. L. (2023). Clinical pharmacological considerations in an early intravenous to oral antibiotic switch: are barriers real or simply perceived?. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, *29*(9), 1120–1125.

Early IV-to-oral switch

The NEW ENGLAND JOURNAL of MEDICINE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

OVIVA

Parallel-group, randomized (1 : 1), open-label, non-inferiority trial

1054 participants

PO versus IV in the first 6 weeks

Oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks for complex orthopedic infection, as assessed by treatment failure at 1 year

Li H-K, Rombach I, Zambellas R, Walker S, et al. Oral versus intravenous antibiotics for bone and joint infection. New Eng J Med 2019; 380:425-36.

Early IV-to-oral switch

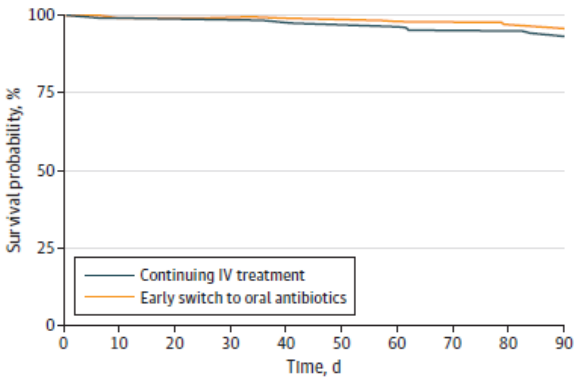
JAMA Network Open

Original Investigation | Infectious Diseases

Early Switch From Intravenous to Oral Antibiotics for Patients With Uncomplicated Gram-Negative Bacteremia

433 Early switch ≤ 4 days vs 481 Prolonged IV

Figure 2. Weighted Survival Curves for Individuals Who Continued or Switched to Early Oral Antibiotics



No. at risk

Continuing IV treatment	481	367	346	340	333	327	323	319	318	315
Early switch to oral antibiotics	433	381	378	375	371	370	366	365	360	360

Medial age: 73 vs 76

Tingsgård, S., Israelsen, S. B., Jørgensen, H. L., Østergaard, C., & Benfield, T. (2024). Early switch from intravenous to oral antibiotics for patients with uncomplicated gram-negative bacteremia. JAMA network open, 7(1), e2352314-e2352314.

Early IV-to-oral switch

More coming:

- The INVEST Trial
- The SOAB Trial
- The GOAT Trial
- and so on…….

Hurdles

- Misbelief
- Lack of awareness
- Lack of time
- Relied on past clinical experience
- Worried about legal consequence
- Moral injury

Misbelief:

1. IV route more effective
2. IV route has better tissue penetration
3. The broader the better
4. The longer the safer

. . . there's two resonant messages that all the frontline staff get and the first one is, 'Don't miss sepsis'. 'If you miss it, you'll be thrown under the bus'. . . . . And then, the other side is: 'But we don't want you to prescribe antibiotics unnecessarily because the vast majority of children have viruses.' . . . . . I think generally the people I work with have a very good understanding of driving resistance by misuse of antibiotics. But I think there's this contradictory message of the fear of not using antibiotics in a life-threatening situation and getting it wrong . . . (Expert Interview 24, paediatric physician)

Davis, M. D. M., Schermuly, A., Rajkhowa, A., Hardefeldt, L., Thursky, K., & Flowers, P. (2024). Risk individualisation and moral injury in the treatment of infection as impediments to the tackling of antimicrobial resistance. *Health, Risk & Society, 26*(5–6), 222–239.

Sendi, P., Nelson, S. B., Soriano, A., & Spellberg, B. (2023). Early switch from intravenous to oral anti-microbial therapy in infectious diseases. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 29(9), 1117–1119.

UK Health Security Agency

Antimicrobial Intravenous-to-Oral Switch (IVOS) Decision Aid

Based on the National Antimicrobial IVOS Criteria

Co-produced through a UK-wide multidisciplinary consensus process involving 279 participants

Why use this IVOS decision aid?

IVOS is an important antimicrobial stewardship intervention.[1,2] Research evidence confirms several IVOS benefits, including decreased risk of bloodstream and catheter-related infections, reduced equipment costs, carbon footprint and hospital length-of-stay, increased patient mobility and comfort, and released nursing time to care for patients.[3,4]

When to use this IVOS decision aid?

The audit standard recommended for the implementation of this decision aid is that all patients on intravenous (IV) therapy should be reviewed promptly from first dose of IV antimicrobial with formal review completed within 48 hours and daily thereafter, unless clearly documented exemptions.

Does your patient have an infection that may require special consideration?

Infections that may require special consideration include: deep-seated infections, infections requiring high tissue concentration, infections requiring prolonged intravenous antimicrobial therapy or critical infections with high risk of mortality.

To note: on specialist advice, an IVOS within 48 hours may still be indicated for some patients with these infections.

Infections for special consideration include, but are not limited to, those listed below:

• bloodstream infection	Y/N	• osteomyelitis	Y/N
• empyema	Y/N	• severe or necrotising soft tissue infections	Y/N
• endocarditis	Y/N	• septic arthritis	Y/N
• meningitis	Y/N	• undrained abscess	Y/N

If YES → check for clearly documented plan or seek specialist advice

If NO → continue

1a. Enteral route

1.1. Is the patient's gastrointestinal tract functioning with no evidence of malabsorption? Y/N

1.2. Is the patient's swallow or enteral tube administration safe? Y/N

If NO → reassess in 24 hours

If YES → continue

1b. Enteral route continued

1.3. Are there any significant concerns over patient adherence to oral treatment? Y/N

1.4. Has the patient vomited within the last 24 hours? Y/N

If YES → reassess in 24 hours

If NO → continue

2. Clinical signs and symptoms

2.1. Are the patient's clinical signs and symptoms of infection improving? Y/N

If YES → continue

If NO → reassess in 24 hours

3. Infection markers

3.1. Has the patient's temperature been between 36-38°C for the past 24 hours? Temp: ..... Y/N

3.2. Is the patient's Early Warning Score (EWS) decreasing? EWS: ..... Y/N

3.3. Is the patient's White Cell Count (WCC) trending towards the normal range?* WCC: ..... Y/N

3.4. Is the patient's C-Reactive Protein (CRP) decreasing?* CRP: ..... Y/N

If NO → reassess in 24 hours

If YES → prompt or assess for switch

PROMPT FOR SWITCH:

Nursing/pharmacy teams to prompt prescriber or infection specialist to consider IV to oral switch.

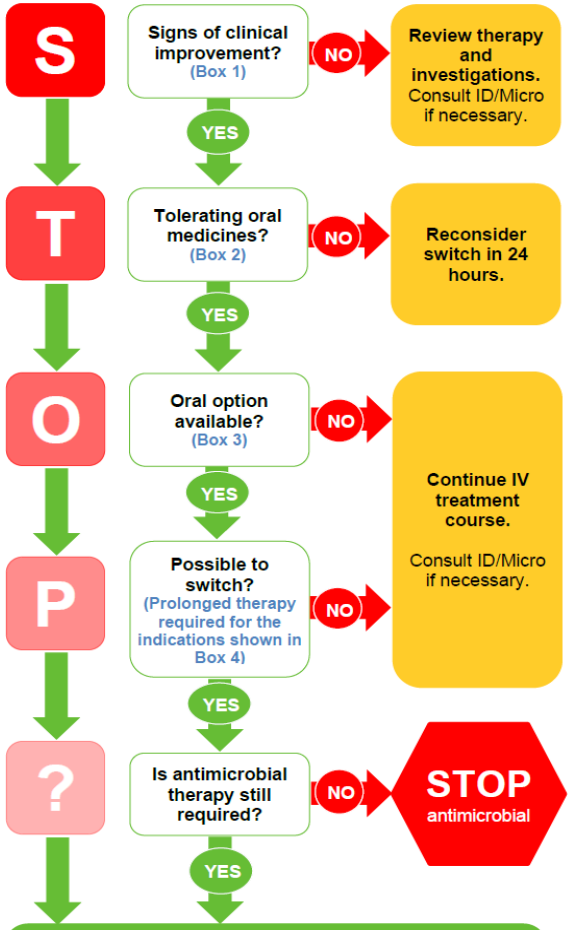
ASSESS FOR SWITCH:

Prescriber or infection specialist to consider IV to oral switch. Identify whether a suitable oral switch option is available, considering for example oral bioavailability, any clinically significant drug interactions, patient allergies or contra-indications.

Intravenous antimicrobial initiation:	Date: __/__/____	Time:	Name: .....
IVOS first assessment (daily thereafter):	Date: __/__/____	Time:	Name: .....
IV to Oral Switch:	Date: __/__/____	Time:	Name: .....

* To note: These infection markers could also indicate inflammation or be affected by for example, steroid treatment, 'Prompt for switch' or 'Assess for switch' may still occur if they are the only markers not met.

Patients who have negative blood cultures and have received ≥ 48 hours of IV therapy may be eligible to STOP or switch to oral therapy
Use this guideline to select appropriate patients – important exclusions apply (see Box 4)



Box 1

Signs of clinical improvement (must meet ALL criteria)

- Afebrile (temp > 36°C and < 38°C for past 48 hours)
- CRP trending down
- Stable immune response (WCC > 4 and < 12 x 10^9 cells/L or trending towards normal range
- No unexplained tachycardia
- No unexplained hypotension
- No tachypnoea

Box 2

Tolerating oral medicines (must meet ALL criteria)

- Patient is not nil by mouth and there is no concern for aspiration (e.g., impaired consciousness)
- Patient is tolerating oral food or enteral feeding*
- Oral absorption is not compromised (e.g., diarrhoea, vomiting, malabsorptive disorder, recent GI surgery, colostomy, swallowing disorder)

**Enteral feeding: consult pharmacy for advice on suitable formulation and administration method*

Box 3

Common oral antimicrobial options

Use the following guide to select appropriate oral therapy. Refer to relevant antimicrobial guidelines where available for preferred oral options for specific indications, e.g., community acquired pneumonia.

Note: Doses provided are for normal renal function – refer to the *Australian Medicines Handbook* or the *Therapeutic Guidelines: Antibiotic* for dosing in renal impairment.

Current IV therapy	Oral option (adult doses)
Amoxicillin 500mg – 1g TDS	Amoxicillin 500mg – 1g TDS
Amoxicillin with clavulanic acid 1.2g TDS	Amoxicillin 875mg with clavulanic acid 125mg BD
Benzylpenicillin 600mg – 1.2g QID	Amoxicillin 500mg – 1g TDS
Ceftriaxone 1g – 2g DAILY	Amoxicillin 875mg with clavulanic acid 125mg BD^
Cefazolin 1g – 2g TDS	Cefalexin 500mg – 1g QID
Ciprofloxacin 200mg – 400mg BD	Ciprofloxacin 500mg – 750mg BD
Clindamycin 600mg TDS	Clindamycin 150mg – 450mg TDS
Flucloxacillin 1g – 2g QID	Di / flucloxacillin 500mg – 1g QID
Metronidazole 500mg BD	Metronidazole 400mg BD or TDS
Piperacillin with tazobactam 4.5g TDS or QID	Amoxicillin 875mg with clavulanic acid 125mg BD **Pseudomonas:** seek advice from Clinical Microbiology or Infectious Diseases
Amoxicillin + gentamicin ± metronidazole	Amoxicillin 875mg with clavulanic acid 125mg BD or 500mg/125mg BD or TDS
Cefepime, gentamicin, meropenem, vancomycin	Seek advice from Clinical Microbiology or Infectious Diseases
The following IV drugs have equivalent oral doses: azithromycin, linezolid, fluconazole, trimethoprim/sulfamethoxazole	

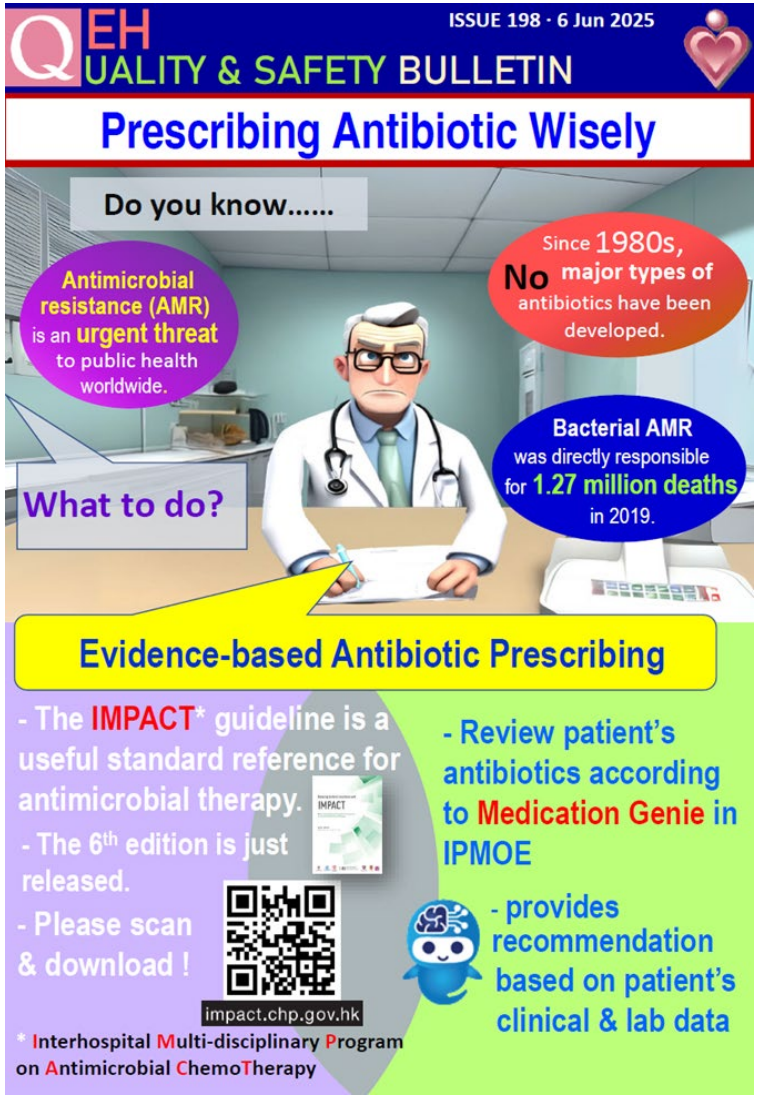
^Consider patient allergy status when converting to a penicillin

Box 4

Prolonged parenteral therapy IS required for the following indications

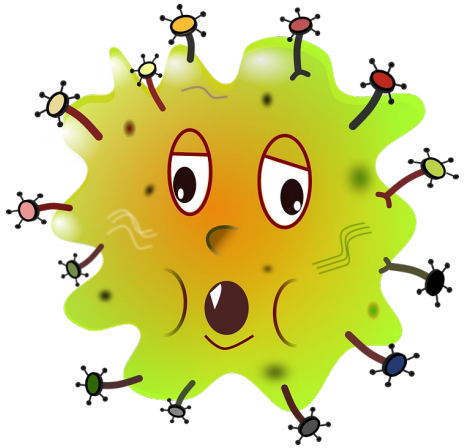
- Deep-seated infection e.g., abscess/empyema
- Meningitis or encephalitis
- Necrotising soft tissue infection
- Infected implant or prostheses
- *Staphylococcus aureus* bacteraemia
- Osteomyelitis
- Septic arthritis
- Endocarditis

What could we do further?

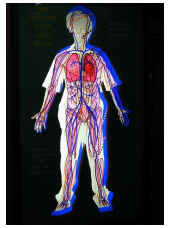


No ‘One Size Fits All’

- Multi-factorial dependency



Identity
Susceptibility



Types and Site of Infection
Source control

Oral bioavailability
Drug-drug Interaction

Age/Comorbidities
Swallowing
GI condition

A.I. / Machine Learning ?

Bolton, W. J., Wilson, R., Gilchrist, M., Georgiou, P., Holmes, A., & Rawson, T. M. (2024). Personalising intravenous to oral antibiotic switch decision making through fair interpretable machine learning. Nature communications, 15(1), 506.

What could we do further?

- Antimicrobial Stewardship
  - Recruit antimicrobial data from pharmacists
  - Proactively discuss with case doctors concerning antimicrobial use
  - Development of Proxy Indicators
- Infectious Disease Consults
  - Causes of persistent fever
  - Appropriate antimicrobials
  - OPAT
  - Early IV-to-oral switch
- Antimicrobial Allergy Delabelling

Take Home Message

- ‘Shorter is better’ and ‘Oral is the New IV’ are supported by robust evidence
- Continued and concerted effort from all parties are of utmost importance

Thank You !