The Challenges of Antibiotic Use in Critically Ill Patients

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Antibiotic usage in COVID 19 Pandemic

- **The impact of coronavirus disease (COVID)-19 on the amount of antibiotic usage and <u>stewardship practice</u> is still not clear** [1,2]

- Based on data taken from a rapid review & meta-analysis of studies through April 2020 [3]

  - **The incidence of bacterial infection in COVID 19 patients**
    - 7% of hospitalized patients
    - **8% of critically ill hospitalized patients**

In fact….

Antibiotics were administered to about **70% of hospitalized COVID-19 patients** and **80% - 100% of those in ICUs** [1,2,3]

Pandemic COVID-19 might trigger antibiotic over-use

1. Clancy CJ, Nguyen MH. 1 May 2020. COVID-19, superinfections and antimicrobial development: What can we expect? Clin Infect Dis. https://doi.org/10.1093/cid/ciaa524
2. Clancy CJ, Buehrle DJ, Nguyen MH. 17 Jul 2020. PRO: The COVID-19 pandemic will result in increased antimicrobial resistance rates. JAC-AMR. https://doi.org/10.1093/jacamr/dlaa049
3. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, Soucy JR, Daneman N. 22 Jul 2020. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. https://doi.org/10.1016/j.cmi.2020.07.016

Penggunaan antibiotik pada COVID 19 sulit dikendalikan dipicu oleh ketidakpastian dan kebingungan di kalangan klinisi…

REVIEW   **Open Access**

The rising problem of antimicrobial resistance in the intensive care unit

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Antibiotic Resistance in the ICU

Time to Take Things Seriously!

The fear of bacterial resistance often drives **overuse of broad-spectrum antimicrobials…**

Penelitian Rhee dkk :

- Populasi sampel : **17.430** pasien sepsis dengan kultur positif
- Sebanyak 15.183 telah dilakukan tes kepekaaan, 12.398 (81,6%) mendapat antibiotik yang tepat → **hanya < 30% disebabkan MDRB**
- *Unnecessarily broad-spectrum treatment* (yang ditujukan untuk meng "cover" MRSA, VRE, ceftriaxone-resistant GNB) **terjadi pada 8.405 (67,8%)** kasus.
- ***Adjusted OR*** untuk kematian di RS adalah **1,27** (1,06–1,4) saat dibandingkan antara kelompok *"unnecessarily" broad-spectrum* dengan *"**not** unnecessarily" broad-spectrum*
- *Unnecessarily broad antibiotic therapy* → **↑ kejadian AKI dan CDI**

Rhee C, Kadri SS, Dekker JP, Danner RL, Chen HC, Fram D, et al. Prevalence of antibiotic-resistant pathogens in culture-proven sepsis and outcomes associated with inadequate and broad-spectrum empiric antibiotic use. JAMA Netw Open. 2020;

Dilemma in deciding on empirical antibiotic therapy in critically ill patients..

Using antibiotics may <u>improve individual patient outcome</u>, but <u>will induce selection pressure</u> and <u>potential harm to future patients</u> or <u>to the same patient in the future</u>, whereas **withholding antibiotics** will <u>avoid selection pressure</u> but may <u>put the individual patient at increased risk of harm</u> caused by an untreated infection.

Reducing Antibiotic Use in the ICU: A Time-Based Approach to Rational Antimicrobial Use
P. O. Depuydt, L. De Bus, and J. J. De Waele

Clinical presentation of HAI in critically ill patients **may be subtle or atypical** at the time when the decision of whether or not to start antibiotics has to be made.

Moreover, at that time, <u>the causative pathogen is usually not identified</u> **but assumed to be potentially resistant to multiple antibiotics**.

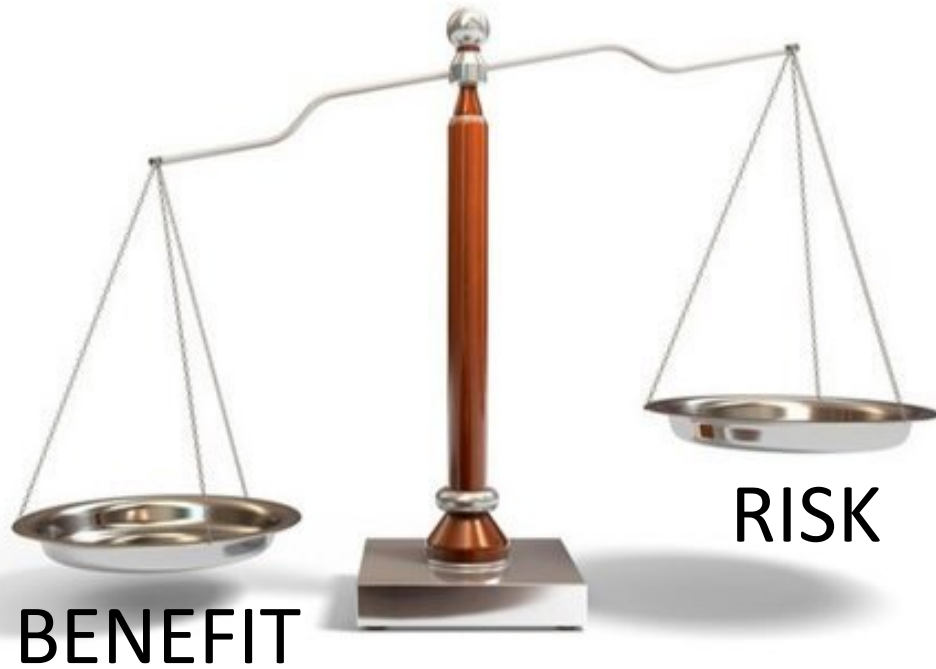**Reducing Antibiotic Use in the ICU: A Time-Based Approach to Rational Antimicrobial Use**
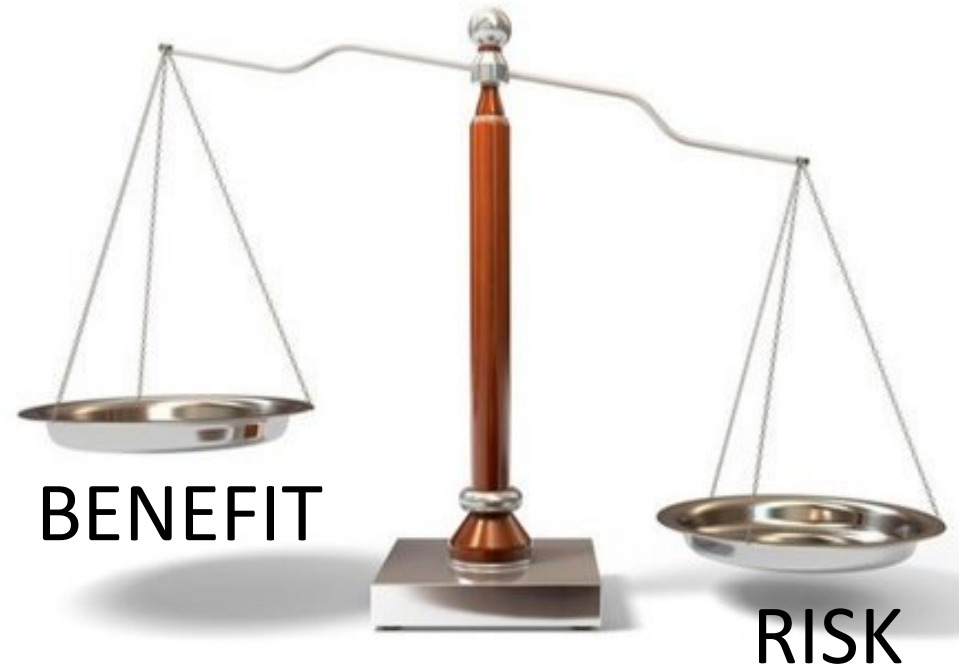P. O. Depuydt, L. De Bus, and J. J. De Waele

Setiap keputusan untuk memberi antibiotik seharusnya selalu dilandasi oleh indikasi yang tepat

Manfaat

Mudhorot

Every decision has consequences..

BENEFIT

RISK

↑ **AMR**

BENEFIT

RISK

↑ **Mortality**

Apakah kita perlu memberi antibiotik ?

Ya

Pasien TERBUKTI mengalami infeksi bakteri
(misalnya dari kultur mikrobiologi didapatkan kuman patogen dengan tingkat yang signifikan, dan kemungkinan besar cocok dengan presentasi klinis)

Gejala klinis pasien konsisten dengan suatu *LIFE-THREATENING INFECTION*
(misalnya diduga meningitis bakteri, *meningococcal sepsis*)

Pasien dengan HIPOTENSI yang kemungkinan disebabkan oleh infeksi

*Wait and See**

Pasien febris dengan sebab belum jelas yang TIDAK mengalami HIPOTENSI

Diduga suatu KOLONISASI kateter dengan organisme yang VIRULENSI nya RENDAH

Pasien dengan ventilator-associated condition (VAC)**

*Wait and See : monitoring ketat untuk mengevaluasi tanda perburukan klinis di ICU/HCU, sementara pemeriksaan tambahan dan upaya untuk mencari dan mengendalikan sumber infeksi dilakukan

**VAC: Peningkatan kebutuhan PEEP dalam 24 jam sebesar 3 cmH$_2$O atau peningkatan FiO$_2$ minimun 20% dari *baseline* dalam 24 jam terakhir, setelah setting ventilator yang stabil dalam 48 jam.

Antibiotic Timing

*Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness, and immediate treatment of acute conditions that can mimic sepsis. Whenever possible, this **should be completed within 3 hours of presentation** so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely anti-microbial therapy provided if the likelihood is thought to be high.*

	Shock is present	Shock is absent
Sepsis is definite or probable	✓ Administer antimicrobials *immediately*, ideally within 1 hour of recognition.	✓ Administer antimicrobials *immediately*, ideally within 1 hour of recognition.
Sepsis is possible	✓ Administer antimicrobials *immediately*, ideally within 1 hour of recognition.	✓ Rapid assessment* of infectious vs. noninfectious causes of acute illness. ✓ Administer antimicrobials *within 3 hours* if concern for infection persists.

Society of Critical Care Medicine
The Intensive Care Professionals

ESICM

Impact of inappropriate empiric antimicrobial therapy on outcome in *Pseudomonas aeruginosa* bacteraemia: a stratified analysis according to sites of infection

E.-J. Joo · C.-I. Kang · Y. E. Ha · S. Y. Park · S.-J. Kang · Y. M. Wi · N. Y. Lee · D. R. Chung · K. R. Peck · J.-H. Song

Abstract

Background ...

... of the inappropriate
im... ...53.8%] vs. 23/72

... ...piric antimicrobial
...e of the independent risk
...o [OR] 8.69; 95% confidence interval
...0.59), along with renal disease, corticosteroid
a... ...polymicrobial infection and higher Pitt bacteraemia
R... score.

ae... ...piric
ant... ...nce in the
30-... the inappropriate
thera... ...te therapy group (19/80
[23.8... ...%], *P* = 0.692). Patients with
pneum... ...i-hepatobiliary tract intra-abdominal
infecti... ...wed significant association with high mortal-
ity, while those with urinary tract or hepatobiliary tract
infection showed negative associations with mortality. In
the subgroup analysis including 98 patients with high-risk

Conclusion Inappropriate empiric antimicrobial therapy adversely affected the outcome of *P. aeruginosa* bacteraemia in patients with high-risk sites of infection. Our data suggest that the impact of inappropriate antimicrobial therapy on the outcome of *P. aeruginosa* bacteraemia may be dependent on the primary site of infection.

Keywords *Pseudomonas aeruginosa* · Bacteraemia · Treatment outcome · Risk factors · Anti-infective agents

Terapi awal antibiotik mungkin **tidak adekwat**, apabila :

- Pemberiannya "terlambat"
- Antibiotik tidak bisa meng"cover" kuman² patogen penyebab infeksi
- Kuman patogen resisten terhadap AB yang diberikan
- **Paling sering**, DOSIS TIDAK ADEKWAT

Chart: Mortality (%) comparison between patients receiving delayed vs timely appropriate antibiotic therapy

- Patients receiving **delayed** appropriate antibiotic therapy
- Patients receiving **timely** appropriate antibiotic therapy

Study	Delayed	Timely
Kollef et al. 1999	42%	18%
Lodise et al. 2007	44%	19%
Kollef et al. 2012	98%	62%
Zasowski et al. 2016	45%	15%
Harris et al. 2018	12%	4%

KPRA RSUD Dr.Soetomo

14

Prinsip Penggunaan Antibiotik "BIJAK" di ICU

- Ambil **kultur sebelum pemberian antibiotik** bila memungkinkan
  - Ambil dari dua tempat berbeda, BUKAN dari akses intravena
  - Waktu pengambilan kultur darah saat demam BUKAN hal penting

- **Jangan menunda pemberian antibiotik**

- *EMPIRICAL THERAPY FIRST; NARROW the spectrum LATER*

- **Pastikan dosis awal adekwat**
  - *under-dosing* harus dihindari
  - *gunakan monoterapi bila memungkinkan (kendali mutu, kendali biaya)*

- **Bila hasil kultur mikrobiologi menunjukkan penurunan kepekaan → pertimbangkan apakah secara klinis antibiotik bekerja.** *Jika secara klinis bekerja → dilanjutkan walaupun tidak cocok dengan bukti laboratorium*. Sensitivitas *in vitro* tidak selalu memprediksi efek *in vivo*

Lipman, J. Principles of antibiotic use. Chapter 72 in Oh's Intensive Care Manual

- Durasi pemberian lebih pendek (misal 7-10 hari) mungkin memberi luaran yang sama dengan pemberian standar 2 minggu. Selalu diskusikan dengan tim pada kasus yang "meragukan".
- **Pahami PK/PD antimikroba.** Pertimbangkan penetrasi ke jaringan dan penyesuaian dosis bila diperkirakan ada perubahan klirens
- **Batasi penggunaan untuk tujuan PROFILAKSIS untuk situasi yang tepat.**
- Pertimbangkan penyebab inflamasi non-infeksi (kondisi yang menyerupai sepsis seringkali terjadi)
- Ikuti aturan pengendalian infeksi
- Jalankan program penatagunaan antibiotik di ICU

Lipman, J. Principles of antibiotic use. Chapter 72 in Oh's Intensive Care Manual

Pemahaman PK,PD, dan PK/PD sangat penting

PK

Dose of ATB
A
D
M
E

→

Plasma concentration changing in time

PD

Concentration in non targeted site ↔ Toxicity

MIN

Concentration in action site ↔ Therapeutic effect

MAX
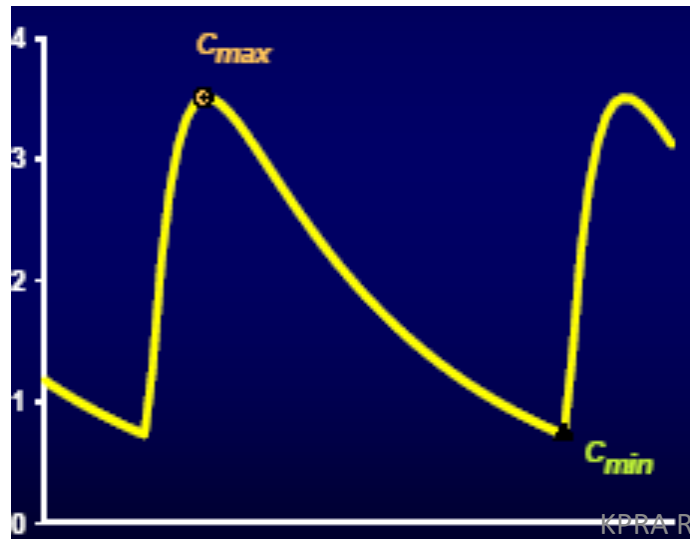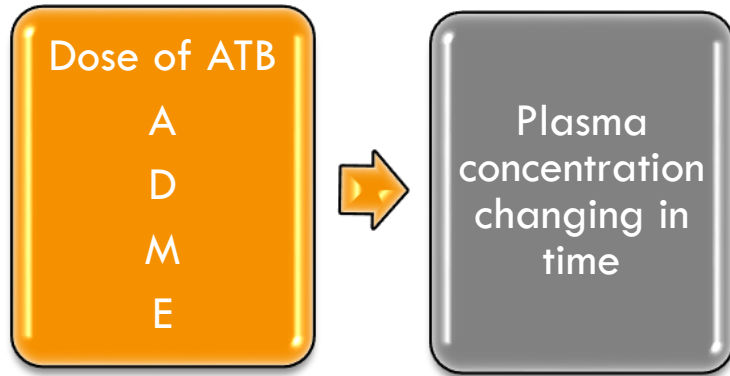
- Protein binding
- C_{max} & C_{min}
- Half-life
- Tissue penetration
- Distribution

C_{max}

C_{min}

W.A. Graig
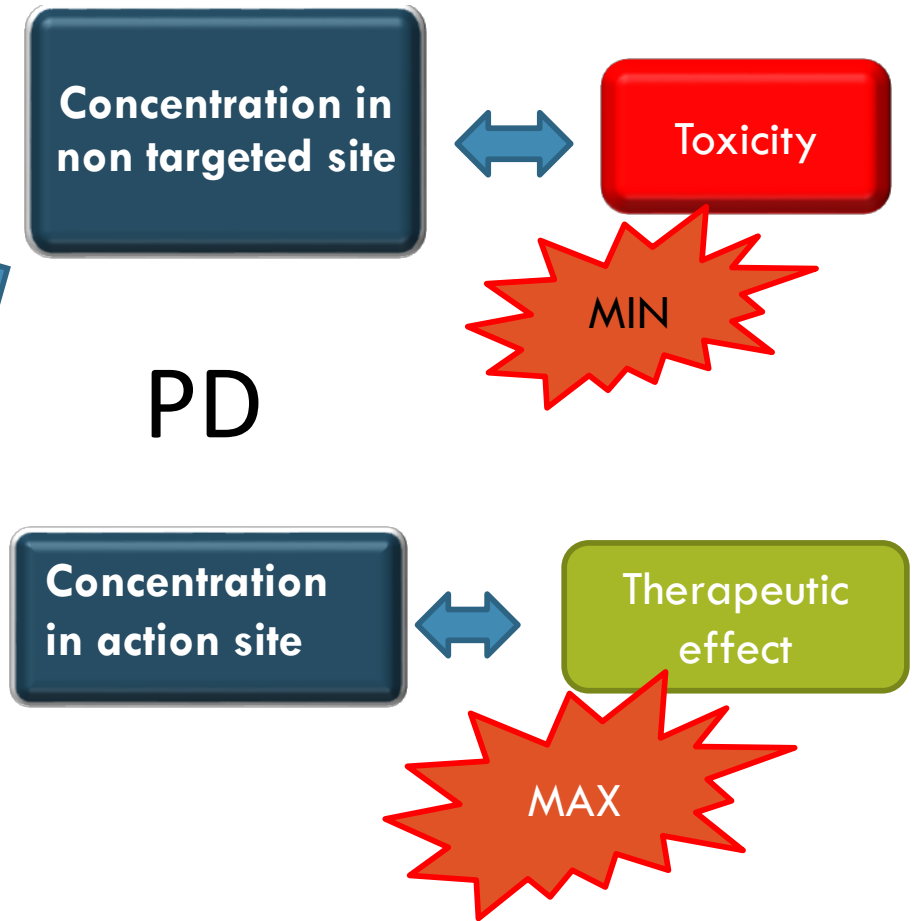
Kesalahan Umum dalam Penggunaan Antibiotik

- **Penundaan pemberian antibiotik pada sepsis atau syok septik**
- Memberikan antibiotik sebelum diambil kultur, tanpa alasan yang rasional
- Sampel terkontaminasi (cara pengambilan yang salah) atau tidak cukup jumlahnya (terutama sampel darah)
- **Penggunaan antibiotik berkepanjangan tanpa alasan yang jelas**
- **Mengubah antibiotik tanpa alasan yang rasional (erratic)** pada sepsis yang tidak membaik
- **Dosis tidak adekuat**

Lipman, J. Principles of antibiotic use. Chapter 72 in Oh's Intensive Care Manual

- **Pemilihan antibiotik empirik yang tidak tepat**, karena kesalahan menginterpretasi hasil kultur mikrobiologis (antibiotik untuk kuman komensal atau kolonisasi)
- **Tidak mampu memprediksi adanya toksisitas** atau memperkirakan kemungkinan **interaksi obat**
- **Tidak mempertimbangkan penetrasi jaringan** saat memilih antibiotik untuk terapi
- Penggunaan **kombinasi antibiotik yang TIDAK TEPAT** atau tidak melakukan de-eskalasi ke monoterapi

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Evaluasi respons pasien saat memberi terapi antibiotik

Infeksi/sepsis/syok septik
Klinis + (leukosit, procalcitonin, CRP.
X-ray toraks, LP, CT - scan, dll)

- Kultur mikrobiologis
- Gram stain

Suhu ^{0}C

Antibiotik

Penyesuaian terapi

?

37,5

Demam dan tanda infeksi lain menetap

- Kesadaran
- Deteksi komplikasi
- Monitor gejala infeksi

Leukosit, PCT, CRP.
Foto toraks
LP, CT-scan

- **Komplikasi**
- **Fokal infeksi lain**
- **Resisten antibiotik**
- **Dosis suboptimal**
- **Rute tidak tepat**
- **Salah diagnosis**
- *Drug fever*
- *Perlu source control*

0   1   2   3   4   **5**   6   7   8

Hari rawat
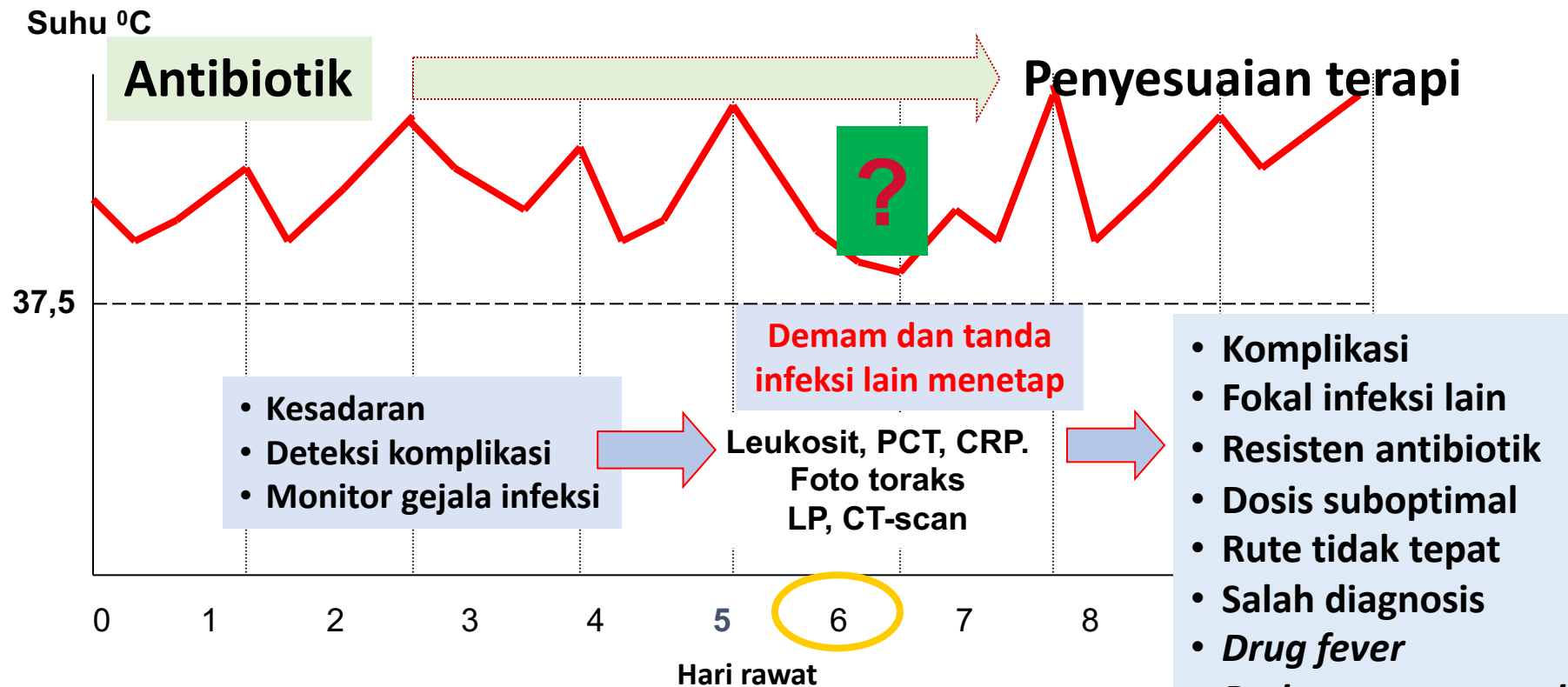
Source control is important part of resuscitation in SEPSIS ...

"Infectious foci suspected to cause septic shock should be controlled as soon as possible following successful initial resuscitation"

Inappropriate source control within 6-12 hours

Survival rate

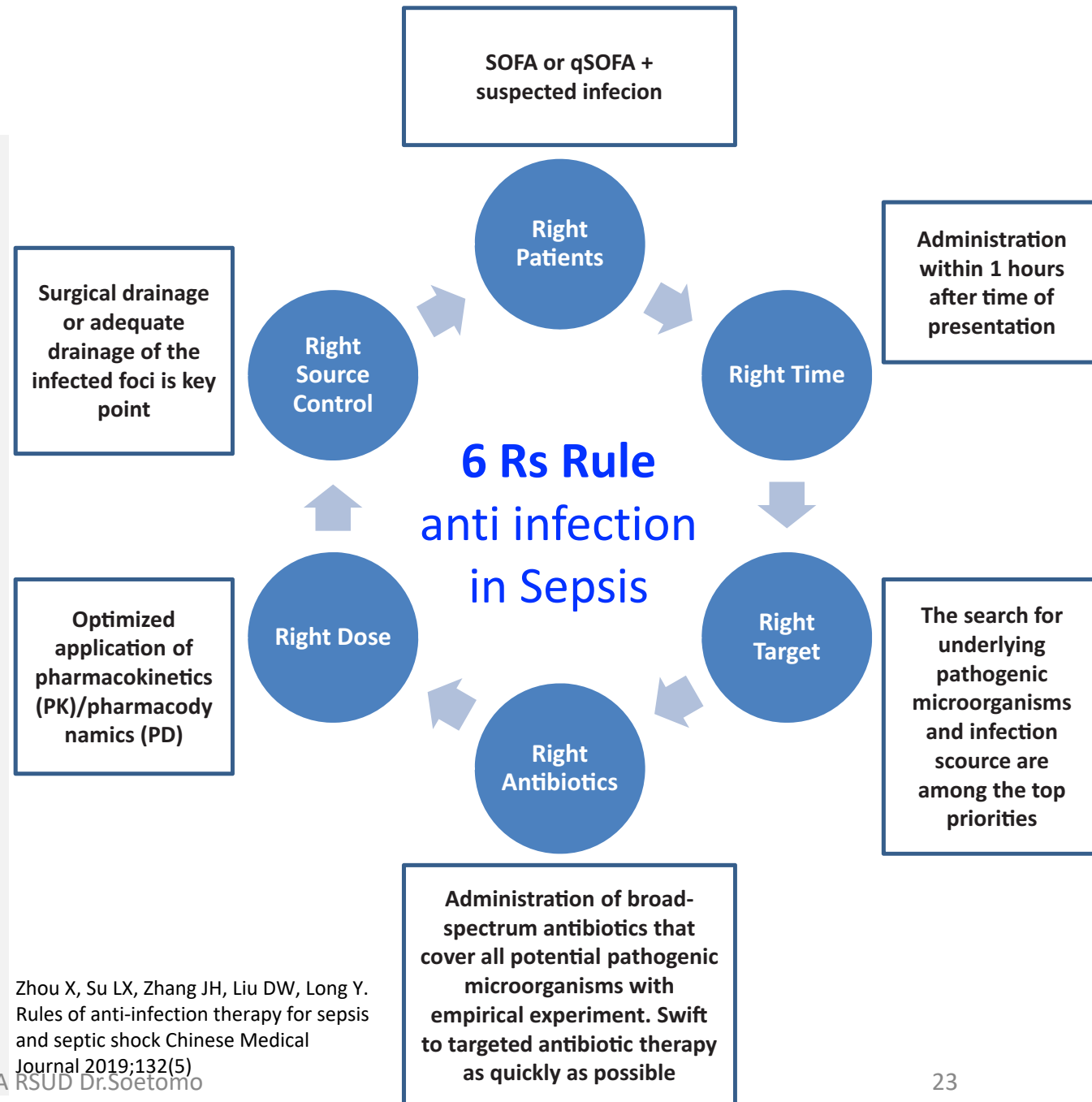# Fokus-fokus infeksi yang memerlukan "source control"

Abses → **drainase**

Jaringan nekrotik → *debridement*/**amputasi**

CLABSI/CAUTI, SSI → **melepas alat-alat invasif atau** *implant* **yang berpotensi menjadi sumber infeksi**

Ulcus decubitus → **mengendalikan secara definitif kontaminasi mikroba yang masih berlangsung (nekrotomi dan** *wound care***)**

Six *Rights* Rule

1. **Right patients** : skrining cepat dan diagnosis dini
2. **Right time** : *"time is life"*
3. **Right target** : identifikasi secara tepat sumber infeksi dan kuman pathogen merupakan kunci keberhasilan terapi
4. **Right antibiotics** : memilih antibiotik secara rasional
5. **Right dose** : menerapkan secara optimal terapi antibiotik berdasarkan pemahaman PK/PD
6. **Right source control** : mengendalikan/eradikasi sumber infeksi sangat vital untuk mengoptimalkan efek terapi antibiotik

SOFA or qSOFA + suspected infecion

Right Patients

Administration within 1 hours after time of presentation

Right Time

6 Rs Rule
anti infection
in Sepsis

Surgical drainage or adequate drainage of the infected foci is key point

Right Source Control

Right Target

The search for underlying pathogenic microorganisms and infection scource are among the top priorities

Optimized application of pharmacokinetics (PK)/pharmacodynamics (PD)

Right Dose

Right Antibiotics

Administration of broad-spectrum antibiotics that cover all potential pathogenic microorganisms with empirical experiment. Swift to targeted antibiotic therapy as quickly as possible

Zhou X, Su LX, Zhang JH, Liu DW, Long Y. Rules of anti-infection therapy for sepsis and septic shock Chinese Medical Journal 2019;132(5)

Take home message

Prinsip terapi antibiotik pada pasien kritis :

- **Lakukan RESUSITASI yang adekwat**

- Tetapkan diagnosis definitif (**infeksi**) sebelum memberi antimikroba

- *Source control* adalah bagian dari resusitasi pada sepsis

- Terapi antibiotik **empirik** awal yang TEPAT

    - berikan dengan dosis dan rute pemberian yang tepat, jangan ditunda, dan jangan berlebihan

- *Streamlining antibiotic*

- **Batasi penggunaannya**

- **Pahami PK, PD, and PK/PD**

- Terapkan standar PPI yang ketat dan penatagunaan antibiotik di ICU

TERIMA KASIH