Medicines Shortages – Causation and Approaches to Improvements The Clinical Needs

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Conflict of Interest

- Nothing to disclose


PUTNIK
SIRONA

INSTITUT ZA ORTOPEDSKO-HIRURŠKE BOLESTI

"BANJICA"

1961

Outline

- Real cases
- Clinical needs vs clinical risks
- Clinical risk management
- Antimicrobial shortages
- Life-saving medicine shortages

Case: Morphine Injection Shortage

- When hydromorphone is introduced as an alternative:
- An IV of HYDROmorphone prescribed at the intended dose to replace morphine resulting in the death of two patients
- A HYDROmorphone 0.5 mg IV was to be substituted for morphine 4 mg IV, but a HYDROmorphone 4 mg IV was given in error
- A patient switched from a morphine 6 mg IV to HYDROmorphone but no change in the dose. The patient received several 6 mg doses, which required naloxone administration and increased the length of hospitalization

CLINICAL NEED (how much? how potent? how long?)

Institute for Safe Medication Practices. Drug shortages: national survey reveals high level of frustration, low level of safety. ISMP Medication Safety Alert! Acute Care. September 23, 2010; 15: 1–6

Case: No Propofol on the Horizon …

- Methohexital was given as an alternative agent for deep sedation instead of propofol:
- Unfamiliarity with diluting and dosing methohexital resulted in the death of a patient
- A paralyzed, ventilated patient received no sedation since propofol was not available and an alternative drug was never prescribed
- Prolonged hospitalization from intractable post-op nausea and vomiting has occurred with alternative sedation agents
- Inadequate sedation with benzodiazepines led to agitation and self-extubation where one patient bit through her tongue

CLINICAL NEED (how much? how potent? how long?)
How agitated is the patient?
Postoperative nausea?
Vomiting related sedative?

Institute for Safe Medication Practices. A shortage of everything except errors: harm associated with drug shortages. ISMP Medication Safety Alert! Acute Care. 2012; 17: 1–4

What to Bare in Mind - Thiopental

- Alternative medicines or techniques
- Thiopental sodium
- HEED CAUTION when used as an alternative to propofol!
- Not an anti-emetic
- Does not suppress laryngeal and airway reflexes as effectively as propofol
- Causes severe tissue necrosis if extravasated in intra-arterial injection crystals form causing distal ischaemia
- Longer elimination half-time; unsuitable for rapid recovery after infusion or accumulated boluses
- CONTRA-INDICATED in patients with porphyria or barbiturate allergy

National Essential Anaesthesia Drug List (NEADL), The Association of Anaesthetists, 2015.

What to Bare in Mind - Etomidate

HEED CAUTION when used as an alternative to propofol:

- A glucocorticoid should be given to cover adrenal suppression lasting up to 24 hours after a single dose
- Not an anti-emetic
- Involuntary movements, rigidity, coughing, hiccoughing and larygospasm much more likely than with propofol (50% vs 10%)
- Pain on injection, venous thrombosis and thrombophlebitis are particularly problematic
- Lethal as a sedative infusion for critically-ill patients

National Essential Anaesthesia Drug List (NEADL), The Association of Anaesthetists, 2015.

Key Messages

- Substitution needs to take into account individual patient-clinical needs as much as possible
- Dosing, reconstitution, route of administration should not be conducted automatically compared to the original treatment
- If a substitute is not the optimal option, aditional monitoring should be a must after an alternative is introduced to a patient
- Timing plays a crucial role in substituting a medicine depending on the disease and the patient’s clinical condition

Case: Piperacilin/Tazobactam Shortage

- What should we look for when determining an alternative medicine?
- antibiotic spectrum of activity
- formulary cost
- local bacterial / susceptibility patterns
- What do we need to do when the physician wants to switch to cefepime (+/-metronidazole) or a formulary carbapenem?
- Provide corresponding information taking into account clinical needs

Duke antimicrobial stewardship outreach network (dason), Drug Shortages: Focus on Piperacillin/Tazobactam (ZosynTM), 2015.

But What if There Is no Cefepime?

- Alternatives to cefepime also exist but have significant limitations:
- Ceftriaxone offers good Gram-positive and Gram-negative activity, but does not cover P. aeruginosa
- Ceftazidime offers good Gram-negative activity, including Pseudomonas spp, but also has the drawback of poor Gram-positive activity. It also lacks anaerobic activity and might lead to a higher incidence of ceftazadime-resistant Pseudomonas spp

Valiquette L, Laupland KB. Antimicrobial shortages: Another hurdle for clinicians. The Canadian Journal of Infectious Diseases & Medical Microbiology. 2015;26(2):67-68.

But What if There Is no Cefepime?

- Carbapenems can provide a similar spectrum of activity to piperacillin/tazobactam
- There are 2 major limitations in the practice of substituting piperacillin/tazobactam for carbapenems:
- Promoted development of most multi-drug resistant organisms, such as carbapenem-resistant Enterobacteriaceae (CRE), associated with high mortality, nosocomial-outbreaks, and poor patient outcomes
- More costly than piperacillin/tazobactam.

Valiquette L, Laupland KB. Antimicrobial shortages: Another hurdle for clinicians. The Canadian Journal of Infectious Diseases & Medical Microbiology. 2015;26(2):67-68.

Flumazenil - Who gets it and Who Doesn't?

Key changes include:

- Physicians should be aware of the shortage of flumazenil (0.1 mg/mL 5 mL injection)
- Conserve flumazenil injection for those requiring mechanical ventilation except for the contraindications as indicated below:
- Accidental pediatric ingestion with compromised airway and breathing
- Intentional self-poisoning with present compromised airway and breathing when skills and equipment to intubate are not readily available
- Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures

Covenant Health. Pharmacy Services. Flumazenil 0.1 mg/mL 5 mL injection SHORTAGE, 2017.

COMMENTARY

Prince didn't need to die; an opioid antidote was available in naloxone

Those at risk of overdose should be given training and access to this remedy, which is a simple nose spray.

By Evan Rausch | APRIL 22, 2017 — 12:45AM

Naloxone 0.4 mg in 1 ml

Clinical Indications - Complete or partial reversal of opioid sedation, including respiratory depression

Alternative drugs or techniques:

1. Naltrexone
2. Buprenorphine

- Naloxone has an extremely high affinity for μ-opioid receptors and can produce rapid onset of withdrawal symptoms if not carefully titrated to effect
- Naltrexone is structurally similar but has a slightly increased affinity for κ-opioid receptors over naloxone, which can only be administered enternally
- Buprenorphine is a partial agonist and could be used to reduce but not reverse μ-receptor stimulation

National Essential Anaesthesia Drug List (NEADL), The Association of Anaesthetists, 2015.

Clinical Need vs Clinical Risk

Clinical Need

“The input needed to reduce risk and achieve predicted outcomes, which approximates to the amount of clinical input needed.”

Clinical Risk

“The degree to which foreseeable harm can be managed by your intervention.”

Kate Malcomess,

the Care Aims Intended Outcomes Framework Founder

Clinical Need – met or unmet?

If NO

handling risks

- Clinical risks divided into two areas:
- medication errors
- adverse patient outcomes

The potential harm of the substitute will depend on the clinical situation/clinical need we NEED to assess

Drug Shortages: A Complex Health Care Crisis Fox, Erin R. et al. Mayo Clinic Proceedings , Volume 89 , Issue 3 , 361 – 373.

Clinical Need - Delay or Providing a Substitute?

- state of the disease
- medicine
- lengh of time of the delay
- clinically significant delay (vaccines vs antimicrobials?)

Drug Shortages: A Complex Health Care Crisis Fox, Erin R. et al. Mayo Clinic Proceedings , Volume 89 , Issue 3 , 361 – 373.

Unmet Clinical Needs with Emerging Clinical Risks

Chemotherapy — Uncertain outcomes / cure

- Delay in treatment
- Inferior outcomes
- Omitted / reduced doses; rationing / substitution not supported by evidence

Antimicrobials — Toxicity / Safety profile

- Poor outcomes
- Death / decreased therapeutic efficacy

Anestetics — Longer anestesia / Recovery times

- Hypotension, Apnea
- Aspiration / prolonged mechanical ventilation / nausea / vomiting

Drug Shortages: A Complex Health Care Crisis Fox, Erin R. et al. Mayo Clinic Proceedings , Volume 89 , Issue 3 , 361 – 373.

Clinical Needs Assessment

- What is clinical needs assessment?

‘A process by which information is gathered regarding the scope and potential impact of gaps or deficiencies in the current delivery and practice of health care’

Weigl et al. 2012

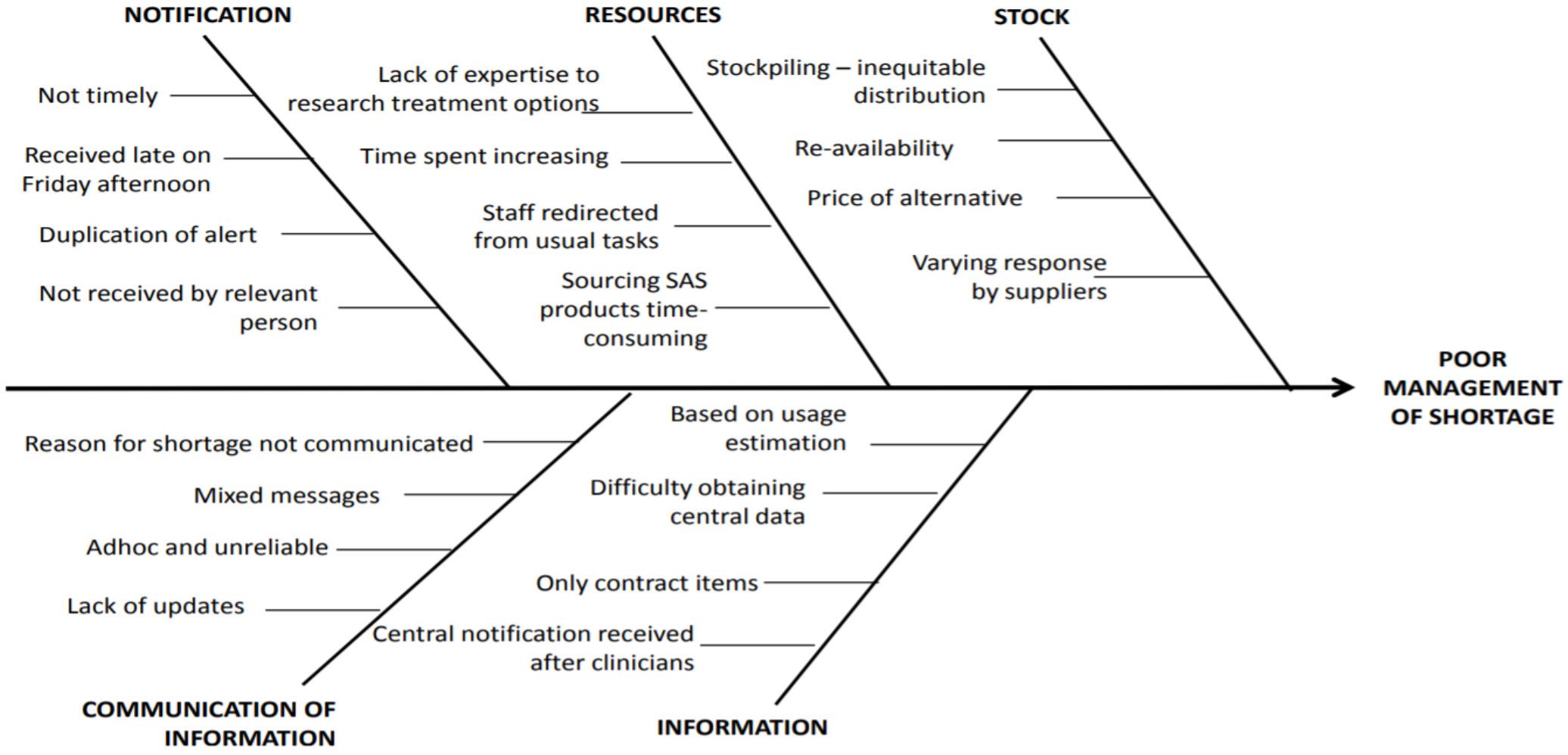
Weigl BH, Gaydos CA, Kost G, et al. The Value of Clinical Needs Assessments for Point-of-Care Diagnostics. Point of care. 2012;11(2):108-113.

Risk Assessment-Why do we Consider Risks?

- Risk associated with the unavailability of a medicine
- Risk associated with replacement medicines

Nina Muscillo, Antimicrobial Shortages Role of the CEC, Clinical Excellence Commission, 2017.

Critical Points to be Considered



Nina Muscillo, Antimicrobial Shortages Role of the CEC, Clinical Excellence Commission, 2017.

Clinical Risk Management

Office of Safety and Quality in Health Care Western Australian Department of Health, Clinical Risk Management Pocket Guide for the Western Australian Health System Information Series No. 8, 2014.

Step 1: Establishing the Context

- Key questions?
- **Has the strategic and organisational context been clearly defined?**
- *Do we know how the system works when a prescriber / health care professional finds out that there is a shortage?*
- **Has the clinical risk evaluation criteria been established?**
- *Do we know on what grounds (indicators) we are assessing risks from a shortage?*
- **Has the clinical risk management framework been established and resources assigned?**
- *Do we know what methodology we are using to quickly assess emerging risks from a shortage?*

Office of Safety and Quality in Health Care Western Australian Department of Health, Clinical Risk Management Pocket Guide for the Western Australian Health System Information Series No. 8, 2014.

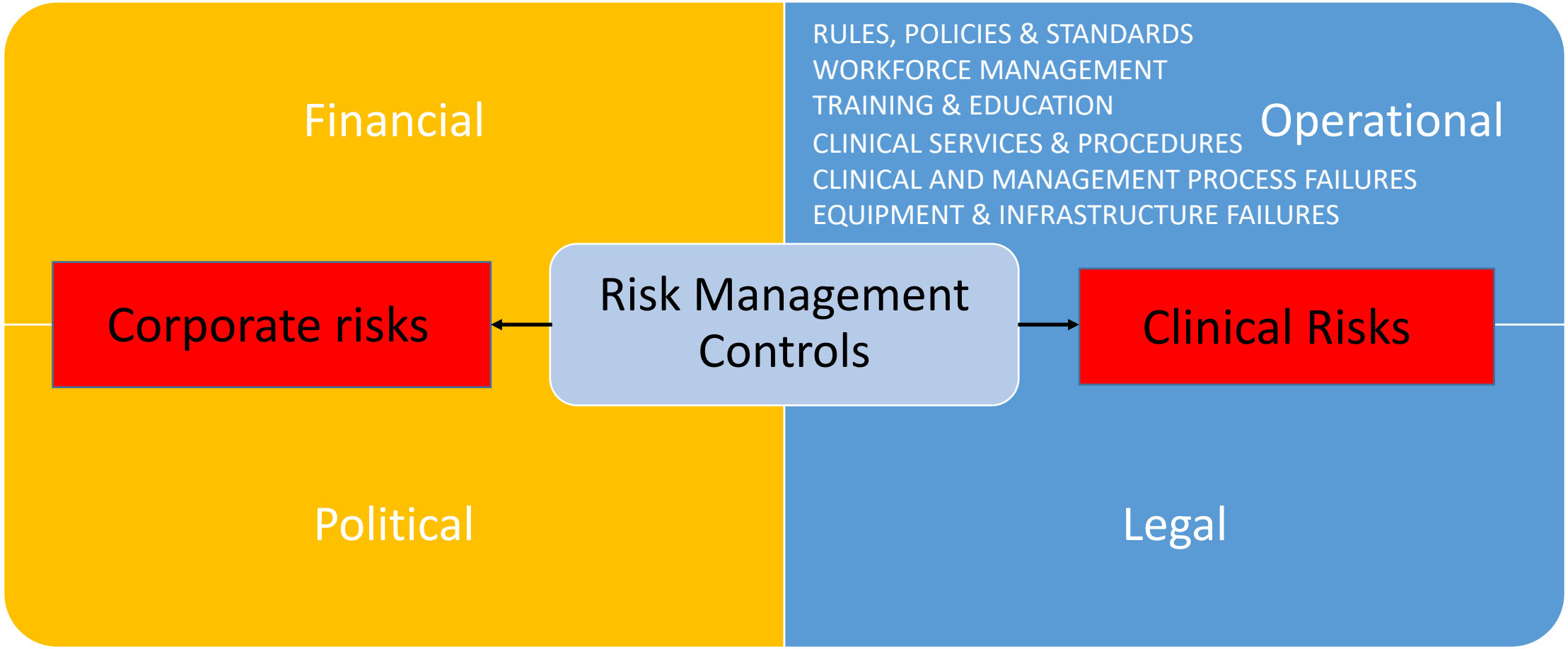
Step 2: Clinical Risk Identification

What if...
But what if...
And then ...

- Identify the likelihood and consequence of actual and potential clinical risks and determine which clinical risks need to be managed and treated as a priority

Office of Safety and Quality in Health Care Western Australian Department of Health, Clinical Risk Management Pocket Guide for the Western Australian Health System Information Series No. 8, 2014.

Step 2: Clinical Risk Identification



Office of Safety and Quality in Health Care Western Australian Department of Health, Clinical Risk Management Pocket Guide for the Western Australian Health System Information Series No. 8, 2014.

Step 3: Clinical Risk Analysis

- Determine the potential consequences and impact of the worst case clinical risks should they occur
- Identify the factors which may increase or decrease clinical risk
- Select the most suitable risk analysis tool and calculate the level of clinical risk

Office of Safety and Quality in Health Care Western Australian Department of Health, Clinical Risk Management Pocket Guide for the Western Australian Health System Information Series No. 8, 2014.

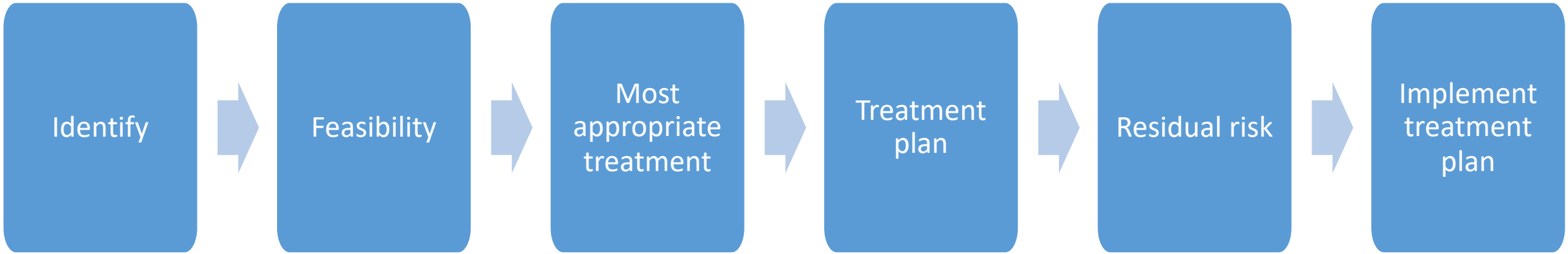
Step 4: Clinical Risk Evaluation

Decide if a clinical risk is acceptable or whether it requires actions to reduce the level of risk

Develop a prioritised list of clinical risks

Office of Safety and Quality in Health Care Western Australian Department of Health, Clinical Risk Management Pocket Guide for the Western Australian Health System Information Series No. 8, 2014.

Step 5: Selection of Options for Treating Clinical Risks



Office of Safety and Quality in Health Care Western Australian Department of Health, Clinical Risk Management Pocket Guide for the Western Australian Health System Information Series No. 8, 2014.

Key Messages

Patients

- Have the right to expect healthcare professionals to be responsible for their care and treatment to be effective regardless of medicine shortages

Health-care professionals

- Develop a deeper understanding of the patients' clinical needs
- Making decisions regarding medicine substitution witihin a multidsicplinary team

CONDITIONS

Drug Shortages: The Scary Reality of a World Without Meds

HEALTH NEWS JANUARY 15, 2016 / 4:47 PM / 3 YEARS AGO

Drug shortages in U.S. emergency rooms on the rise

HUB

JOHNS HOPKINS UNIVERSITY

Health experts offer recommendations to combat shortages of lifesaving drugs

Consensus statement calls for proactive strategy focused on prevention

Recall of Opioid Overdose Drug is the Latest in a Series of Shortages and Backorders

NATIONAL HEALTHCARE

'Patients will die if they don't fix this': Hospitals rationing, stockpiling first-line antibiotics amid drug shortage

TREATMENTS

Critical Drugs For Hospital ERs Remain In Short Supply

May 2, 2016 · 4:17 PM ET

'Unorderly' Brexit risks shortage of life-saving drugs

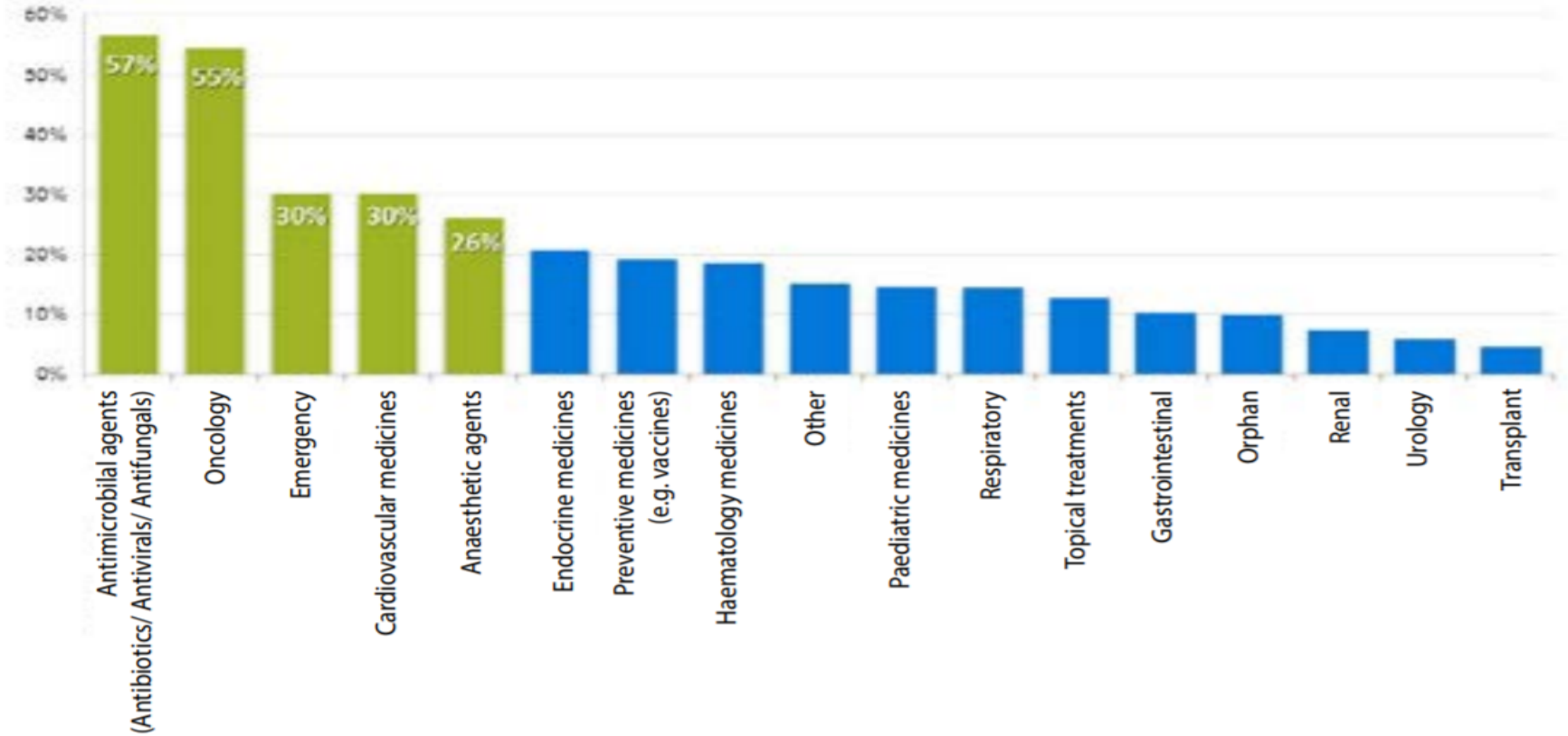
The Pharmaceutical Journal | 13 JUL 2017

A Hospital Pharmacy Reality

A white board showed the drugs in short supply at the University of Utah Hospital in Salt Lake City in 2011.

Jim Urquhart/AP

Antimicrobial Shortages-Europe



EAHP Medicine Shortages Survey 2014

Antimicrobial Shortages

Medicines	Resolved Shortage Time in Days (2001-2013)
With injectable administration	250
Without injectable administration	129
With available alternatives	262
Without availalbe alternatives	149.5
Broad spectrum	232
Narrow spectrun	199.5

Farha Quadri, Maryann Mazer-Amirshahi, Erin R. Fox, Kristy L. Hawley, Jesse M. Pines, Mark S. Zocchi, Larissa May; Antibacterial Drug Shortages From 2001 to 2013: Implications for Clinical Practice, Clinical Infectious Diseases, Volume 60, Issue 12, 15 June 2015, Pages 1737–1742.

Antimicrobial Shortages

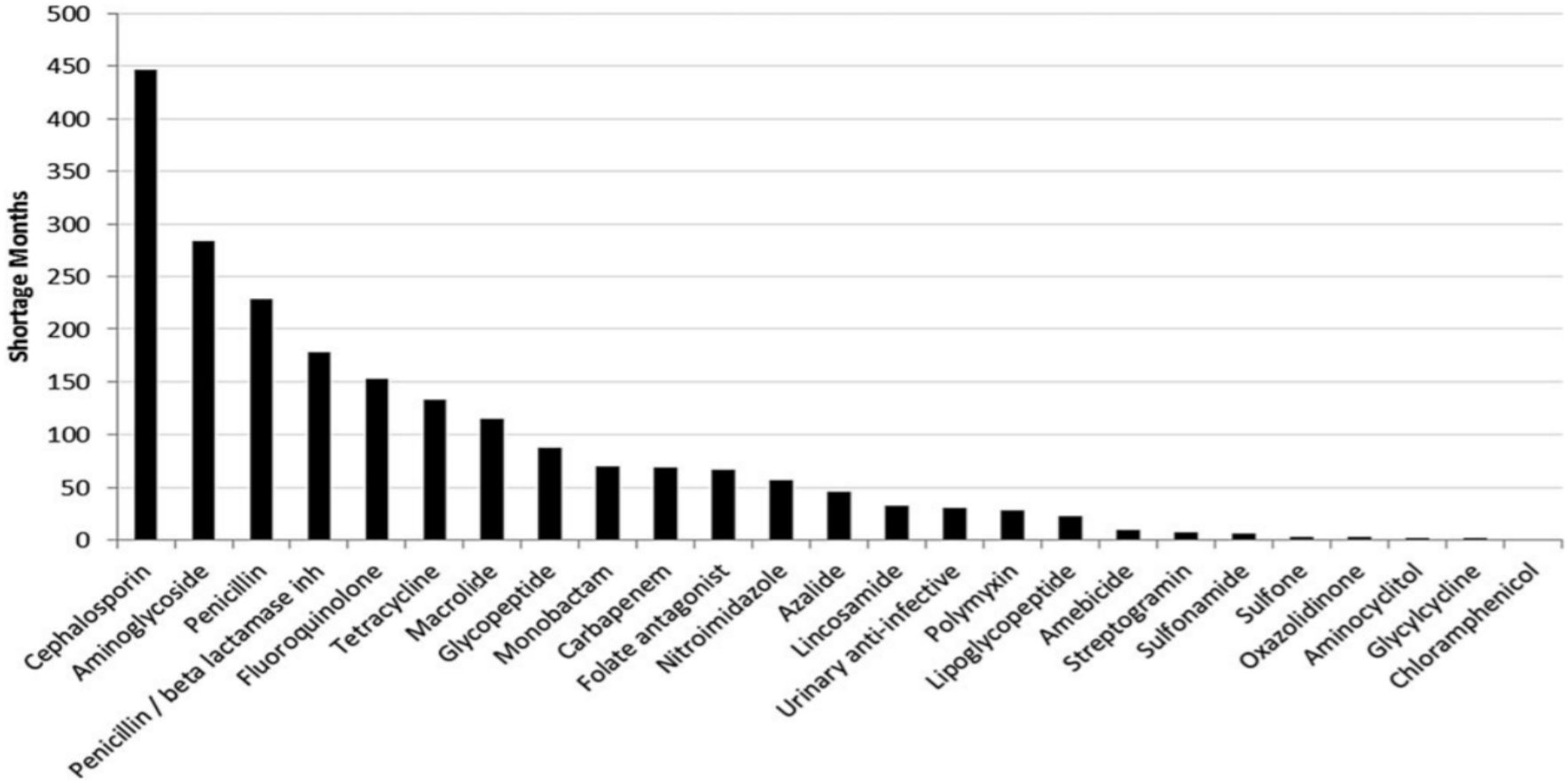
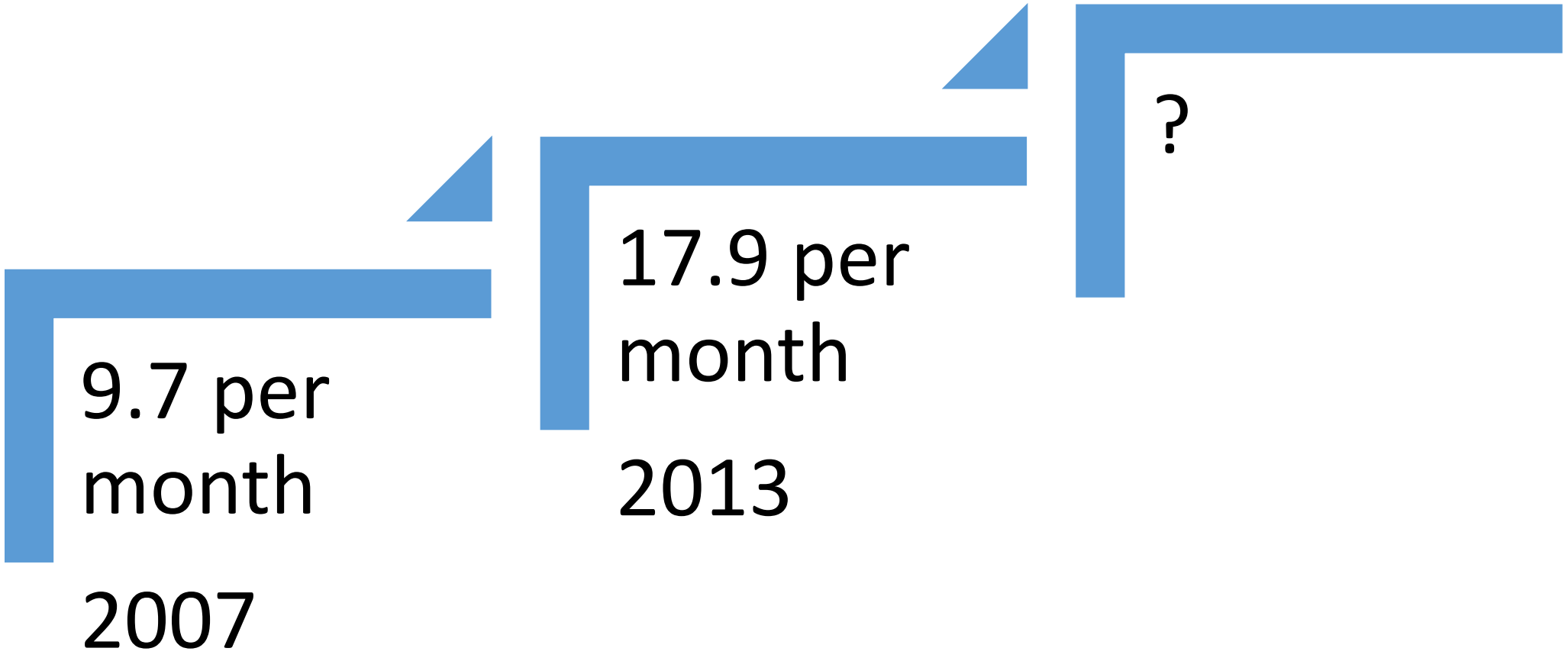


Figure 2. Drug shortages by drug class, 2001–2013.

Source: University of Utah Drug Information Service database

Rise of Antimicrobial Shortages



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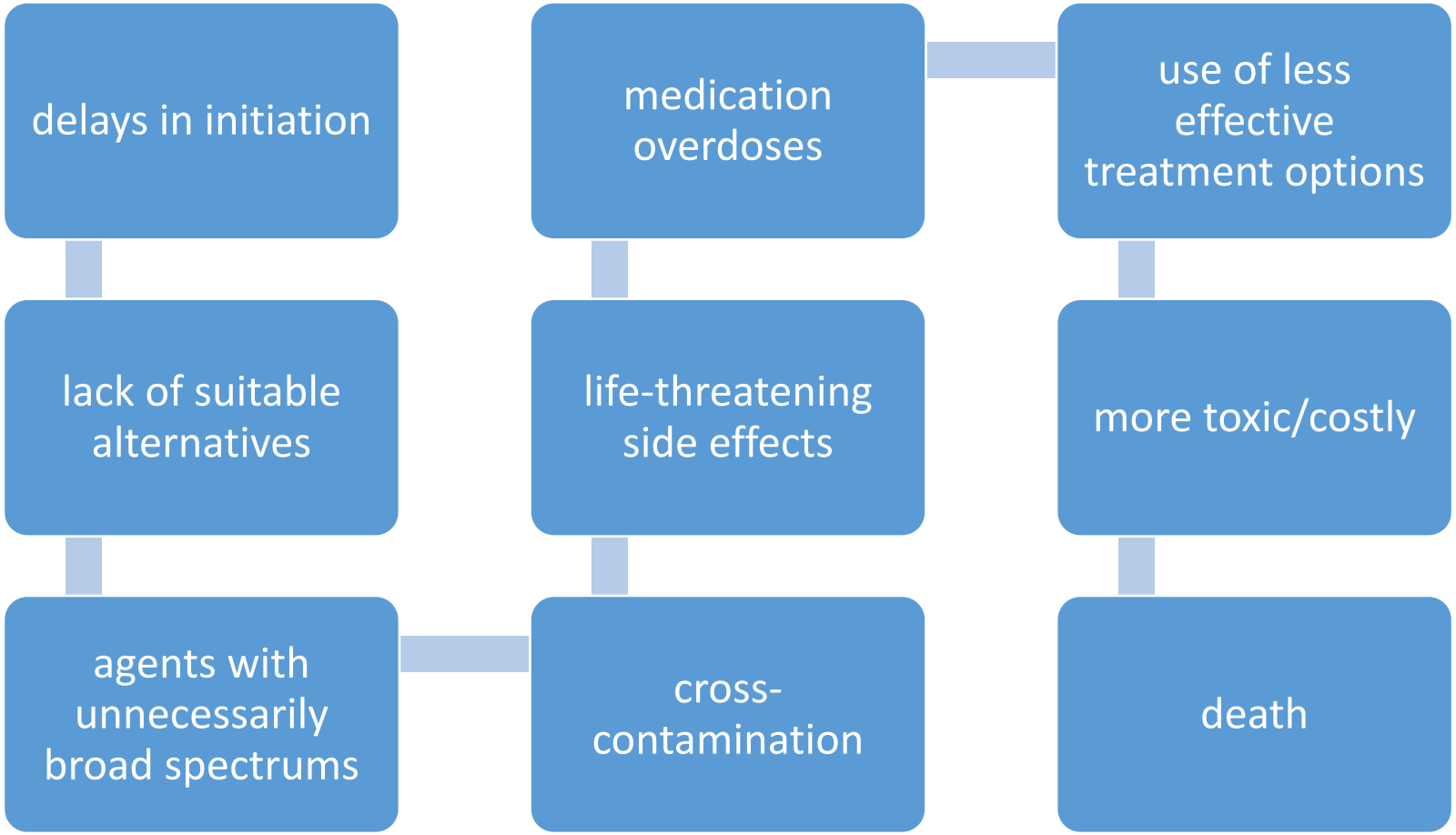
Antimicrobial Shortages

- Broad-spectrum agents-injectable drugs
- Medicines with no alternative sources
- Medicines used on pathogens with limited alternative treatment options or in paediatric patients
- Medicines used to treat highly drug-resistant pathogens

  (including MRSA, CRE, and Pseudomonas)

Farha Quadri, Maryann Mazer-Amirshahi, Erin R. Fox, Kristy L. Hawley, Jesse M. Pines, Mark S. Zocchi, Larissa May; Antibacterial Drug Shortages From 2001 to 2013: Implications for Clinical Practice, Clinical Infectious Diseases, Volume 60, Issue 12, 15 June 2015, Pages 1737–1742.

Antimicrobials Shortages-Implications for the Clinical Management



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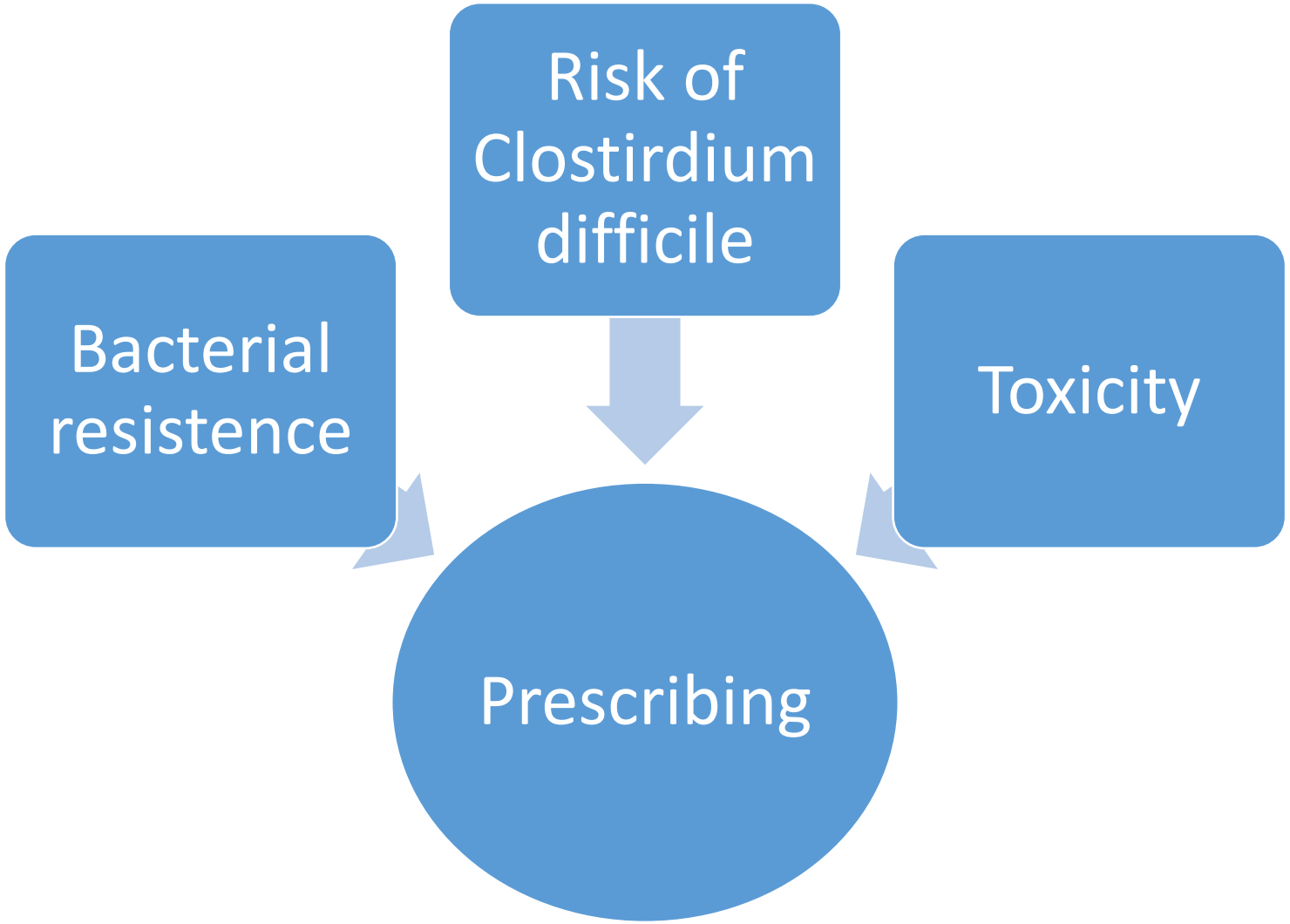
Antimicrobial Shortages



Valiquette L, Laupland KB. Antimicrobial shortages: Another hurdle for clinicians. The Canadian Journal of Infectious Diseases & Medical Microbiology. 2015;26(2):67-68.

Do you have Gentamicin in your Pharmacy?

Maybe tobramicin or amikacin or streptomycin BUT.....

- Enterococcus species are intrinsically resistant to tobramycin and amikacin
- a substantial risk for ototoxicity and vestibular disturbance
- assessment of streptomycin serum concentrations requires special laboratory testing
- increased use of streptomycin could rapidly end in a ‘rebound’ shortage

Valiquette L, Laupland KB. Antimicrobial shortages: Another hurdle for clinicians. The Canadian Journal of Infectious Diseases & Medical Microbiology. 2015;26(2):67-68.

New Cases on the Horizon

IV vancomycin:

Alternative agents: teicoplanin, daptomycin, linezolid & ceftaroline

Risk associated with alternatives:

- Teicoplanin – similar to vancomycin
- Daptomycin – increase CK
- Linezolid – myelosuppression, optic and peripheral neuropathy
- Ceftaroline – neutropenia if treated > 2-3 weeks

Nina Muscillo, Antimicrobial Shortages Role of the CEC, Clinical Excellence Commission, 2017.

New Cases on the Horizon

IV aciclovir:

Alternative agents: ganciclovir, foscarnet & cidofovir

Risk associated with alternatives:

- Ganciclovir – bone marrow suppression
- Foscarnet – decreased renal function and electrolyte abnormalities
- Cidofovir – nephrotoxicity

Nina Muscillo, Antimicrobial Shortages Role of the CEC, Clinical Excellence Commission, 2017.

Emergency Department Medicines

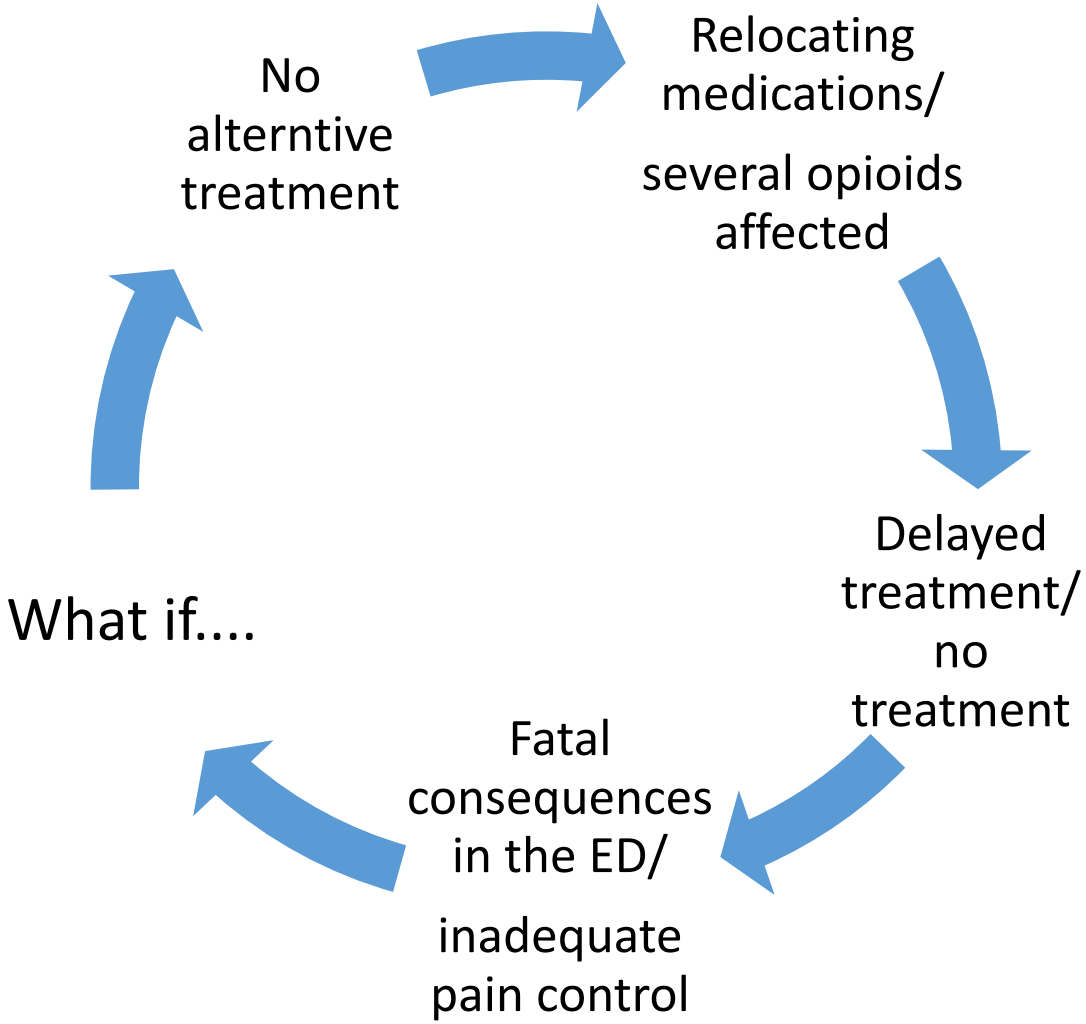
Case: Succinylcholine in Short Supply

Rocuronium may be used but …

- Alternative paralytics may be:
- - less effective than succinylcholine
- - lead to prolonged paralysis
- - suboptimal intubating
- - Increased the risk of complications

Mazer-Amirshahi M, Pourmand A, Singer S, et al. Critical Drug Shortages: Implications for Emergency MedicineAcademic Emergency Medicine 2014;21:704–711.

Delayes



Mazer-Amirshahi M, Pourmand A, Singer S, et al. Critical Drug Shortages: Implications for Emergency MedicineAcademic Emergency Medicine 2014;21:704–711.

Compounding Issues

- Calculating differences between dozes must take into account
- Microbial contamination of compauded products
- Substandard production due to constraints in small-scale pharmacy compounding
- Improper labeling

Mazer-Amirshahi M, Pourmand A, Singer S, et al. Critical Drug Shortages: Implications for Emergency Medicine, Academic Emergency Medicine 2014;21:704–711.

Compromised Sterility and Infectious Complications

Example: 50-mL vials of propofol were reused for multiple patients to conserve the medication, which resulted in the transmission of hepatitis C virus between patients

- Sterile single-use vials of injectable products penetrated multiple times to conserve medication despite violating labeling recommendations

- Improper use can lead to disease transmission between patients, including hepatitis B, C, and the human immunodeficiency virus

Mazer-Amirshahi M, Pourmand A, Singer S, et al. Critical Drug Shortages: Implications for Emergency MedicineAcademic Emergency Medicine 2014;21:704–711.

Key Messages

- Keep local inventory of critical antibacterial agents
- Anticipate the need for alternatives
- Create contingency plans
- Maintain a multidisciplinary antimicrobial stewardship plan
- Create guidelines
- Developing protocols
- Establish an interdisciplinary medicine shortage task force

THANK YOU FOR YOUR ATTENTION