A Pharmacist's Guide to Antimicrobial Stewardship in Asian Hospitals

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Multidisciplinary antimicrobial stewardship (AMS) teams are required to implement and manage the various interventions used as part of hospital AMS programs to promote the optimal use of antibiotics.[1,2] Clinical pharmacists, preferably with infectious disease (ID) pharmacotherapy residency training, are ideally suited to perform many important daily AMS tasks related to the best selection, dosing, route of administration and duration of antibiotic therapy, and should play a prominent role in AMS teams.[1-6]

This guide describes the daily work of the pharmacist within the AMS program, and the role of the pharmacist within the AMS team. The guide is intended to provide ideas and examples of ways to make the best use of pharmacists' expertise in AMS programs. The advice contained in this guide is consistent with evidence-based **guidelines** for the implementation of AMS programs from the Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA)[1] and the American Society of Health-System Pharmacists (ASHP) **statement** on the pharmacist's role in AMS.[4]

Pharmacist involvement in routine AMS tasks

Pharmacists often perform routine AMS program activities (Table 1), including review of antibiotic orders for optimal antibiotic choice, dose, route of administration, duration of therapy, and providing feedback to prescribers regarding appropriateness of therapy and opportunities for intravenous (IV)-to-oral conversion and de-escalation where possible.[2,5-13] Pharmacists may also be responsible for monitoring and reporting AMS **key performance indicators**, such as antibiotic use and costs.[5,7,14,15] AMS pharmacists should ideally have protected time for AMS tasks to prevent the risk of other routine pharmacy services taking priority over AMS.[5-7]

Table 1

IDSA/SHEA-recommended, evidence-based AMS interventions that can be integrated into routine pharmacy services[1,16]

Intervention	Comments
Core interventions	One or both strategies should be included in all AMS programs
Preauthorization	• Certain antibiotics must be approved before they can be prescribed
Prospective audit and feedback	• Prescriptions for audited antibiotics are reviewed after empiric antibiotic therapy has started, with direct feedback and recommendations to continue, adjust, change or discontinue therapy • Aim to review prescriptions within 48 hours of the start of empiric therapy and again in relation to blood culture results (≥72 hours)
Additional interventions	These strategies should be a part of core interventions processes
Hospital-specific guidelines for common infectious disease syndromes	• Help to standardize prescribing practices based on local resistance patterns, evidence-based guidelines and relevant clinical factors • Use to guide and assess empiric treatment choices, de-escalation, IV-to-oral conversion and duration of therapy
De-escalation	• Review patients for opportunities to switch to narrower-spectrum antibiotics or discontinue antibiotics based on clinical criteria and culture results • Choice of antibiotics for de-escalation during empiric therapy can be based on hospital guidelines, while that for pathogen-directed therapy is based on microbiology results
IV-to-oral conversion	• Change antibiotics with good oral bioavailability from the IV to oral route as soon as possible • Relatively simple strategy applicable to many settings
Dose optimization	• Based on patient characteristics, microorganism, site of infection and pharmacodynamic/pharmacokinetic principles of antibiotic agents (consider for broad-spectrum ß-lactams) • Individualized pharmacokinetic monitoring and adjustment for IV antibiotics help ensure adequacy of treatment (consider for aminoglycosides and vancomycin at least, if not for all antibiotics; most important in critically ill patients)

Preauthorization and prospective audit

It is recommended that all AMS programs include some form of preauthorization or prospective audit, or a combination of both.[1,2] These core interventions can be largely pharmacist-driven.[9-12] For example, pharmacists are essential for the success of prospective audit and feedback as part of the AMS program at Singapore General Hospital (SGH) (Figure 1).[12] Pharmacists may also be responsible for assessing the appropriateness of prescriptions for antibiotics requiring preauthorization, and for contacting the prescriber when the prescription does not comply with criteria for approval.[17]

Antibiotics requiring preauthorization or audit are carefully selected based on variables such as:

- Broad-spectrum coverage[12,18]
- Potential to promote resistance[12,18]
- Potential for overuse or misuse[12,18]
- Need to reserve for the treatment of multidrug-resistant infections[18]
- High costs[12,18]
- Risk of serious adverse effects[18]

Carbapenems, fluoroquinolones and glycopeptides are examples of antibiotic drug classes that are often **controlled** in response to high consumption and emergence of resistance to these classes of drugs in Asian hospitals.[2,10,12,15,19,20] The hospital formulary should be regularly **reviewed** and updated in relation to antibiotic consumption and resistance data.[21]

Pharmacist-driven prospective audit and feedback
Singapore General Hospital, Singapore

Pharmacist role

- Review prescriptions of audited antibiotics* on:
  – Day 2 (empiric therapy; within 24 hours of antibiotic prescription)
  – Day 4 (allowing 72 hours for bacterial cultures to be processed)
  – Day 7 and regularly thereafter (if applicable)

- When appropriate, make written and/or verbal recommendations for:
  – IV-to-oral conversion
  – Dose optimization
  – De-escalation

- Only complicated cases are referred to an ID physician for review. See Figure 1 for workflow

Criteria for inappropriate prescription

- Hospital antibiotic guidelines not followed without valid reasons
- IV dose, route, duration and/or empirical treatment choice suboptimal according to hospital guidelines
- Narrower-spectrum antibiotic could be used based on culture results
- No bacterial infection (ie, colonization or alternative explanation for symptoms)
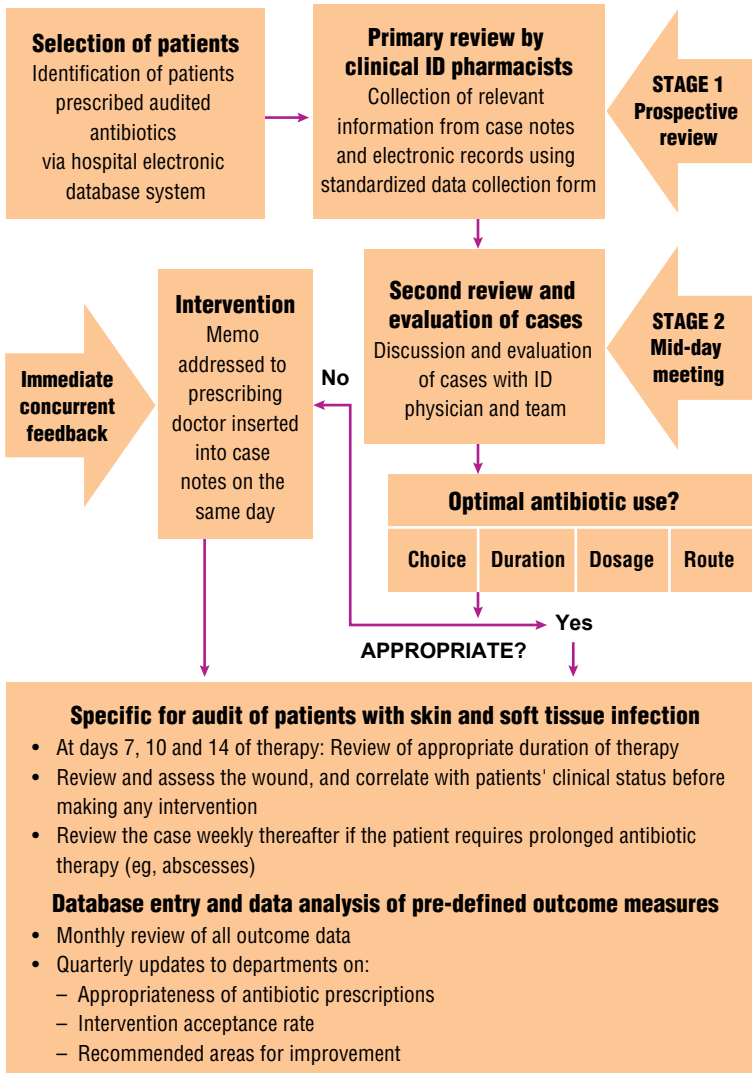
Measured outcomes (intervention-adherent vs non-adherent)

- Reduced audited antibiotic consumption and costs
- Shorter duration of therapy and hospital stay

*Selection criteria: High procurement costs, broad-spectrum coverage and associated high resistance rates, potential for misuse, increasing trends of prescription.

Workflow of the pharmacist-driven prospective audit and immediate feedback system as part of the AMS program at Singapore General Hospital[12,19,23,24]

Selection of patients
Identification of patients prescribed audited antibiotics via hospital electronic database system

Primary review by clinical ID pharmacists
Collection of relevant information from case notes and electronic records using standardized data collection form

STAGE 1 Prospective review

Intervention
Memo addressed to prescribing doctor inserted into case notes on the same day

Immediate concurrent feedback

Second review and evaluation of cases
Discussion and evaluation of cases with ID physician and team

STAGE 2 Mid-day meeting

No

Optimal antibiotic use?

Choice	Duration	Dosage	Route

APPROPRIATE? **Yes**

Specific for audit of patients with skin and soft tissue infection
- At days 7, 10 and 14 of therapy: Review of appropriate duration of therapy
- Review and assess the wound, and correlate with patients' clinical status before making any intervention
- Review the case weekly thereafter if the patient requires prolonged antibiotic therapy (eg, abscesses)

Database entry and data analysis of pre-defined outcome measures
- Monthly review of all outcome data
- Quarterly updates to departments on:
  – Appropriateness of antibiotic prescriptions
  – Intervention acceptance rate
  – Recommended areas for improvement

Adapted from Teo J, et al. 2012; Liew YX, et al. 2012; and Loo LW, et al. 2015.

As is the case at SGH,[12,24] the following AMS tools and strategies are commonly integrated into the pharmacist's antibiotic review process:

- Hospital-specific antibiotic guidelines
- De-escalation
- IV-to-oral conversion
- Dose optimization

Hospital-specific antibiotic guidelines

When they are available, hospital-specific antibiotic treatment **guidelines** should be used by pharmacists as a benchmark to assess the appropriateness of therapy, including antibiotic choice and duration of therapy, and make empiric recommendations for therapy change.[8,24-26] Hospital-specific guidelines can be adapted from general evidence-based practice guidelines from professional societies such as the **IDSA** to suit the hospital formulary and bacterial susceptibility patterns seen on the hospital **antibiogram**.[24,25] Such guidelines usually contain antibiotic recommendations and other helpful advice for commonly treated infections, including but not limited to:

- Community-acquired pneumonia
- Hospital- and ventilator-acquired pneumonia
- Skin and soft tissue infections
- Urinary tract infections
- Intra-abdominal infections
- Sepsis

Empiric vs definitive antibiotic therapy[27,28]

- In the absence of rapid diagnostic testing, which may be cost prohibitive, microbiology results are generally not available for 24 to 72 hours
- Initial antibiotic therapy is, therefore, usually empiric and guided by clinical presentation and the organisms most likely to be causing the infection at that site of infection
- When the pathogen causing the infection is identified, definitive pathogen-directed antibiotic therapy can be started

De-escalation

If the hospital's empiric antibiotic treatment guidelines have not been followed without a valid reason, the pharmacist should recommend that broad-spectrum empiric therapy be de-escalated in clinically stable patients (Table 2).[8,29] For example, carbapenem therapy can be de-escalated in Asian settings where ESBL-producing Gram-negative organisms are endemic.[8] Choice of antibiotics during empirical therapy should be based on hospital guidelines, and tailored to patient characteristics, site of infection, risk factors for multidrug-resistant bacteria, and local microbiology and susceptibility patterns.[8,26] Once microbiology results are available, the pharmacist should encourage the change to definitive therapy with as narrow a spectrum pathogen-directed treatment as possible based on culture and susceptibility results.[8,26,27,29]

Pharmacist-driven carbapenem de-escalation
Tan Tock Seng Hospital, Singapore

Pharmacist role
- Review carbapenem prescriptions on:
  - Days 1 and 2 for appropriate indications and dosage based on evidence-based, hospital-approved guidelines
  - Day 3 onwards for a de-escalation opportunity

- Recommendations for de-escalation where appropriate (Table 2) documented in the patient's chart, including reasons for de-escalation, often with telephone or face-to-face discussions

- Only complicated cases or cases where the primary care team does not accept the ward pharmacist's recommendations are referred to ID physicians for review

Choice of antibiotic for de-escalation
- Hospital antibiotic guidelines for empiric therapy
- Culture and susceptibility results for definitive pathogen-directed therapy

Measured outcomes (de-escalated vs not de-escalated)
- Shorter duration of therapy
- Lower rate of adverse drug reactions
- Lower incidence of carbapenem-resistant *Acinetobacter baumannii* acquisition
- Lower incidence of *Clostridium difficile*-associated diarrhea

Table 2

Criteria for the de-escalation of broad-spectrum antibiotics used by pharmacists during prospective audit and feedback as part of an AMS program at Tan Tock Seng Hospital, Singapore[8]
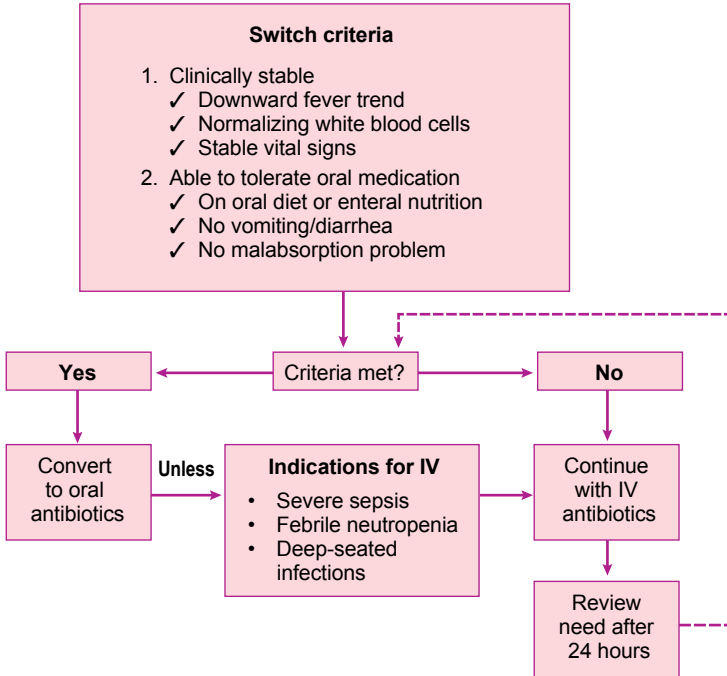
	Empiric therapy	Definitive therapy
Criteria for de-escalation via switching to narrower-spectrum antibiotics	• Temperature <38°C for 24 hours • Not on inotropes • Systolic blood pressure returned to baseline or ≥100 mmHg • Not mechanically ventilated or fraction of inspired oxygen ≤0.4 • Respiratory rate <25 breaths per minute and saturation of oxygen ≥92% on room air	• De-escalation to narrower-spectrum antibiotics based on culture and susceptibility results, in the absence of contraindications
Criteria for de-escalation via discontinuation	• Completed course of therapy • No indication or infectious causes identified	

IV-to-oral conversion

IV-to-oral conversion of the same antibiotic is a relatively simple intervention, and pharmacists should routinely encourage IV-to-oral conversion of antibiotics with good bioavailability in eligible patients (Figure 2).[1,2,13,26] For example, fluoroquinolones are highly bioavailable drugs that can easily be converted from the IV to the oral route of administration.[30] Advantages of oral therapy include ease of administration, early discharge opportunities, decreased IV-related adverse events and drug cost savings.[26]

Figure 2

The IV-to-oral conversion guideline used by pharmacists during prospective audit as part of the AMS program at Singapore General Hospital[12]

Switch criteria

1. Clinically stable
   - ✓ Downward fever trend
   - ✓ Normalizing white blood cells
   - ✓ Stable vital signs
2. Able to tolerate oral medication
   - ✓ On oral diet or enteral nutrition
   - ✓ No vomiting/diarrhea
   - ✓ No malabsorption problem

Criteria met?

Yes → **Convert to oral antibiotics** — Unless → **Indications for IV**
- Severe sepsis
- Febrile neutropenia
- Deep-seated infections

No → **Continue with IV antibiotics** → **Review need after 24 hours**

Adapted from Teo J, et al. 2012.

**Pharmacist-driven IV-to-oral conversion
of fluoroquinolones**
Seoul National University Bundang Hospital, Korea

Pharmacist role
- Identify patients in general wards receiving IV fluoroquinolones for ≥3 days who are able to take oral medication

- Recommend IV-to-oral conversion via a note in the medical record stating:
  – Primary site of infection
  – Purpose of antibiotic administration
  – Type of fluoroquinolone being administered, dose and treatment period
  – Information on oral equivalent dose and drug interactions

Measured outcomes (switched vs not switched)
- Shorter duration of IV and total fluoroquinolone therapy
- Shorter duration of hospital stay
- Lower IV and total fluoroquinolone costs

Dose optimization

Pharmacist expertise in relation to pharmacokinetic and pharmacodynamic principles is particularly beneficial when reviewing antibiotic regimens for dose optimization.[2,31] Dose optimization may not necessarily require therapeutic drug monitoring, and can be implemented by pharmacists on the basis of identifying deviations from recommended dosing schedules, and making recommendations to optimize dosing based on pharmacokinetic and pharmacodynamic principles.[2,12] However, in critically ill patients, dose optimization via therapeutic drug monitoring will help ensure adequacy of treatment.[2,32]

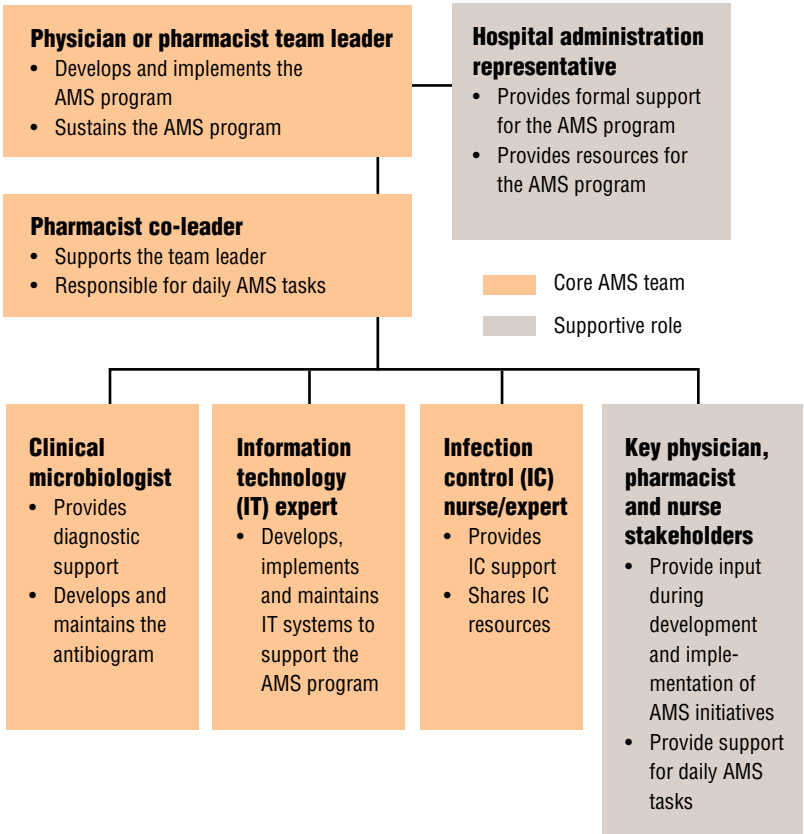## The pharmacist as part of the AMS team leadership structure

It is recommended that a clinical pharmacist, preferably with ID pharmacotherapy residency training, co-lead the AMS team with an ID physician team leader (Figure 3).[1,2] The pharmacist co-leader should support the team leader in their tasks, including:

- The development and maintenance of treatment **guidelines**
- Antibiotic audit and formulary choices
- Providing AMS advice and education to relevant hospital staff

In hospitals where there are no available ID physicians, a clinical pharmacist, preferably with ID pharmacotherapy residency training, may be called on to **lead** the team.[2] In such a setting, the pharmacist is required to **implement** and **sustain** the AMS program.[33]

Figure 3

Suggested hospital AMS team structure and function[2,3,16]

Physician or pharmacist team leader
- Develops and implements the AMS program
- Sustains the AMS program

Hospital administration representative
- Provides formal support for the AMS program
- Provides resources for the AMS program

Pharmacist co-leader
- Supports the team leader
- Responsible for daily AMS tasks

☐ Core AMS team
☐ Supportive role

Clinical microbiologist
- Provides diagnostic support
- Develops and maintains the antibiogram

Information technology (IT) expert
- Develops, implements and maintains IT systems to support the AMS program

Infection control (IC) nurse/expert
- Provides IC support
- Shares IC resources

Key physician, pharmacist and nurse stakeholders
- Provide input during development and implementation of AMS initiatives
- Provide support for daily AMS tasks

Adapted from Apisarnthanarak, et al. 2018; Dellit, et al. 2007; and the Centers for Disease Control and Prevention 2019.

A pharmacist-led AMS program
McKay-Dee Hospital, United States

Setting
- Small community hospital with no ID physician for routine consult
- Easily applied to Asian hospitals with little or no ID physician support

Pharmacist background
- Strong interest and background in ID practice
- No formal post-graduate ID training

Pharmacist role
- 0.9 full-time equivalent
- 6-month pre-implementation lead-in for educational and promotional strategies:
  - Presentations at medical staff meetings
  - Discussions with physicians about perceptions of a pharmacist-led AMS program
  - Education of pharmacy staff regarding the new program and ideas for implementation
  - E-mails to medical staff with updates on implementation of the program
- Routine tasks:
  - Manually review all patients receiving antibiotics with face-to-face discussions with prescribers to make recommendations for:
    » De-escalation
    » IV-to-oral conversion
    » Dose optimization
  - Available by phone to answer after-hours questions relating to antibiotic therapy

- Provide formal and informal education about optimal antibiotic use to hospital staff
- Regularly meet with pharmacy and medical directors, and a hospitalist and intensivist, to receive feedback on how the program could be improved
- Send monthly reports to the pharmacy director and hospital administration detailing interventions made, cost savings, program successes and areas for improvement

Measured outcomes (year before implementation vs after implementation)

- Reduced use of targeted antibiotics, such as carbapenems
- Reduced length of hospital stay for patients with community-acquired pneumonia
- Reduced antibiotic costs

ID training for AMS pharmacists

It is recommended that an AMS pharmacist should ideally have some ID training.[2] If ID-trained pharmacists are unavailable, clinical pharmacists with an interest in but no formal ID training could serve as core AMS team members and take on AMS activities.[2,34] A potential strategy could be to initially have pharmacists with no ID training assist with AMS interventions that require less ID expertise, such as IV-to-oral conversion.[13,34] Non-ID pharmacists in the AMS team could acquire ID knowledge and skills by shadowing pharmacist, physician or microbiology experts; reading key guidelines and articles; attending professional ID conferences; or completing AMS training programs.[34] Furthermore, ID training courses for AMS pharmacists can be established within the hospital.[35]

ID training for clinical pharmacists, and ID pharmacist-enhanced and -led interventions
Thammasat University Hospital, Thailand

Hospital-based pharmacist ID training[35]
- Six 2-hour ID training sessions
- Seven topics:
    1. Definition of appropriate antibiotic use
    2. Common antibiotic drug interactions
    3. Antibiotic de-escalation
    4. Monitoring antibiotic side effects
    5. Structure and organization of the AMS program
    6. Monitoring AMS program outcomes
    7. Examples of antibiotic use recommendations provided by an experienced ID physician
- After the training program, hospital-wide adjunct ID clinical pharmacist consultation was made available[35]
- A pharmacist-led intervention was subsequently studied[36]

Pharmacist role in a pharmacist-enhanced AMS program[35]
After an ID clinical pharmacist consultation request, the ID clinical pharmacist was responsible for:
- Participation in daily rounds with the medical team
- Advice on antibiotic use and potential adverse events
- De-escalation reminders

Measured outcomes (ID clinical pharmacist-enhanced consultation vs standard of care)[35]
- More appropriate antibiotic use
- More de-escalation
- Shorter treatment duration
- Shorter length of hospital stay

Pharmacist-led intervention[36]

- The ID pharmacist routinely performed daily prospective audit and feedback along with bedside discussion
  – Suitable antibiotics were suggested for each patient, with appropriate dose and recommended treatment duration
  – The pharmacist then followed the patient until discharge
  – Additional ID physician consultations requested if inappropriate antimicrobial prescriptions were noted
- Other ID pharmacist tasks:
  – Provision of continuous education regarding appropriate antimicrobial therapy
  – Provision of feedback regarding antimicrobial consumption to nurses and physicians involved in antimicrobial therapy
  – Monitoring patients for guideline adherence every 2 weeks (appropriate indication, dose regimen and duration)

Measured outcomes (ID pharmacist-led intervention vs standard AMS program protocol)[36]

- Higher AMS program guideline adherence for empirical and definitive therapy
- Reduced carbapenem and fosfomycin consumption
- Decreased incidence of multidrug-resistant pathogens
- Trend toward increased rate of clinical cure
- Similar 30-day all-cause mortality and length of stay

Non-ID pharmacists can easily make individual efforts to improve their knowledge of ID- and AMS-related issues.[5,34] This may be achieved by a variety of methods such as:

- Becoming familiar with key evidence-based ID clinical practice guidelines, most of which are available on the IDSA website (**www.idsociety.org/practice-guideline/alphabetical-guidelines/**)
- Making use of educational resources, such as those provided by the ASHP (**www.ashp.org**), Centers for Disease Control and Prevention (**https://www.cdc.gov/antibiotic-use/hcp/educational-resources/ stewardship/index.html**), Society of Infectious Diseases Pharmacists (**www.sidp.org/AMSToolkit**) and Center for Infectious Disease Research and Policy (**www.cidrap.umn.edu/asp**)
- Attending rounds with an ID physician
- Visiting institutions with existing AMS programs, such as SGH which offers a clinical attachment in ID pharmacotherapy for hospital pharmacists (more information can be found at: **https://www.sgh. com.sg/pgahi/attachments/Pages/Pharmacy.aspx**)
- Completing a certification program for pharmacists, such as that provided by the Society of Infectious Diseases Pharmacists (more information can be found at: **www.sidp.org/Stewardship-Certificate**)

Summary

Pharmacists are core members of multidisciplinary AMS teams. The success of AMS programs in Asian hospitals relies on the day-to-day efforts of dedicated pharmacists with and without formal post-graduate ID training. Ideally, AMS should be a collaborative partnership between pharmacists and physicians, with support from other AMS team members.

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