Implementing optimal stewardship strategies to combat antibiotic resistance

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Effective MDT management for infection control

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Why is a multidisciplinary team approach needed for antimicrobial stewardship?

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An expert MDT is needed to implement an AMS

AMS focus: prevention, diagnosis and treatment of infection[1]

Core MDT*

- Consultant microbiologist[1,2]
- Infectious diseases specialist[1,2]
- Acute care physician[2]
- Surgeon[2]
- Senior member of the pharmacy management team[1,2]
- Anaesthetist[2]
- Paediatrician[2]
- Senior nurse[2,3]
- Primary care representative[2,3]
- IT experts[1]
- Local authorities[3]

Key roles[4]

- Leadership
- Accountability & responsibilities
- Monitoring
- Reporting
- Education & training
- AMS actions

*In resource-limited settings or small hospitals, the MDT may comprise less specialized practitioners, such as GPs and non-clinical pharmacists.[1]
AMS, antimicrobial stewardship; GP, general practitioner; IT, information technology; MDT, multidisciplinary team.

1. Mendelson M, et al. *Clin Microbiol Infect.* 2020;26:447–53; 2. Public Health England 2015. Antimicrobial stewardship toolkit for English hospitals. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF (accessed 14 January 2022); 3. Alividza V. *Nurs Times*. 2017;113:22–5; 4. WHO 2019. Antimicrobial stewardship. Available at: www.who.int/publications-detail-redirect/9789241515481 (accessed 14 January 2022).

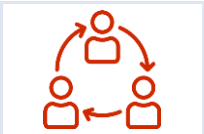
What do you think best practice should be for communication between clinicians so the MDT operates effectively?

Organizational strategies are essential to ensure successful operation of the MDT

A clinical leader must be identified from the core MDT[1,2]

The MDT can reinforce policy implementation

Development of an AMS plan using a framework of behaviour change[2,3]



Coalition building and cross-boundary working[3,4]

Creating a high clinical and managerial profile for infection in the hospital[3,4]

AMS, antimicrobial stewardship; MDT, multidisciplinary team.

1. Mendelson M, et al. *Clin Microbiol Infect.* 2020;26:447–53; 2. Gregory JR, et al. *US Pharm.* 2018;43:HS-7-HS-12;
3. Murray E, Holmes A. *J Antimicrob Chemother*. 2012;67(Suppl 1):i29–36; 4. Kpokiri EE, et al. *Antibiotics.* 2020;9:204.

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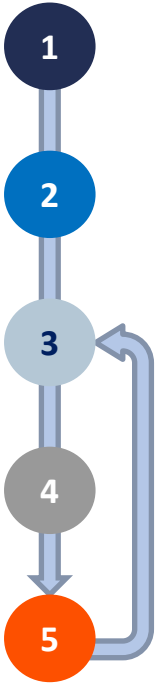
How can clinicians in different countries with different cultures and resources implement an MDT approach to combat antibiotic resistance?

Establishing and measuring success of MDT AMS plan



PREPARE	• Map possible enablers (champions) and barriers (hierarchical healthcare system, resource limitations etc)[1,2] • Engagement with the wider healthcare team, including nurses and pharmacists[1,2]
PLAN	• Present the AMR problem, challenges in antibiotic use and baseline data[1] • Set SMART goals for changing the unit's antibiotic use[1] • Decide on AMS interventions, how to implement them and how to measure change[1]
ACTION	• Implement evidence-based interventions to improve antibiotic use (education, training ward rounds and audit)[1,3]
MONITOR	• Monitor antibiotic prescribing and resistance patterns[3] • Evaluate AMS interventions and their implementation[1] • Review resource use and costs, and determine whether there have been savings[1]
ADJUST	• Report regularly on antibiotic use and resistance to doctors, nurses and clinicians[3] • Agree on any adjustments to interventions, implementation and measurements[1] • Follow up with a continuous improvement cycle[1]

AMR, antimicrobial resistance; AMS, antimicrobial stewardship; MDT, multidisciplinary team; SMART, specific, measurable, achievable, relevant, timebound.

1. WHO 2019. Antimicrobial stewardship. Available at: www.who.int/publications-detail-redirect/9789241515481 (accessed 14 January 2022);
2. Charani E, et al. *PLoS One*. 2019;14:e0209847; 3. Gregory JR, et al. *US Pharm*. 2018;43:HS-7-HS-12.

How can antimicrobial stewardship experts in higher-income and lower- and middle-income countries collaborate to address antimicrobial resistance?

Key factors for implementing AMS programmes

Political commitment and leadership are critical to implement an AMS agenda and provide resources[1]

Global research and development is required on best practices in agriculture, the development of antimicrobials and diagnostic methods[2]

Improved access to amicrobial agents is required in middle- and low-income countries[3]

Global, multi-stakeholder agreement is needed to coordinate resource, engage stakeholders and secure binding commitment for action[2]

AMS, antimicrobial stewardship.

1. WHO 2018. Tackling antimicrobial resistance (AMR) together. Available at: www.who.int/antimicrobial-resistance/publications/Tackling-AMR-multisectoral-coordination-june2018.pdf?ua=1 (accessed 14 January 2022); 2. IACG 2018. Available at: www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_Future_global_governance_for_AMR_120718.pdf (accessed 14 January 2022); 3. Charani E, et al. *PLoS One*. 2019;14:e0209847.

Individualizing patient care for antibiotic-resistant infections

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Spain

What approach should be used for diagnosing microbial infections?

Diagnostic tools for microbial infections

General clinical signs and symptoms

- **Systemic**

- **Peripheral**

- **Vital signs**

Changes in laboratory markers

- **Haematology**

- **Biochemistry**

- **Urinalysis**

- **Microbiology**

Cooley N. *Clin Pharm*. 2010;2:217–20.

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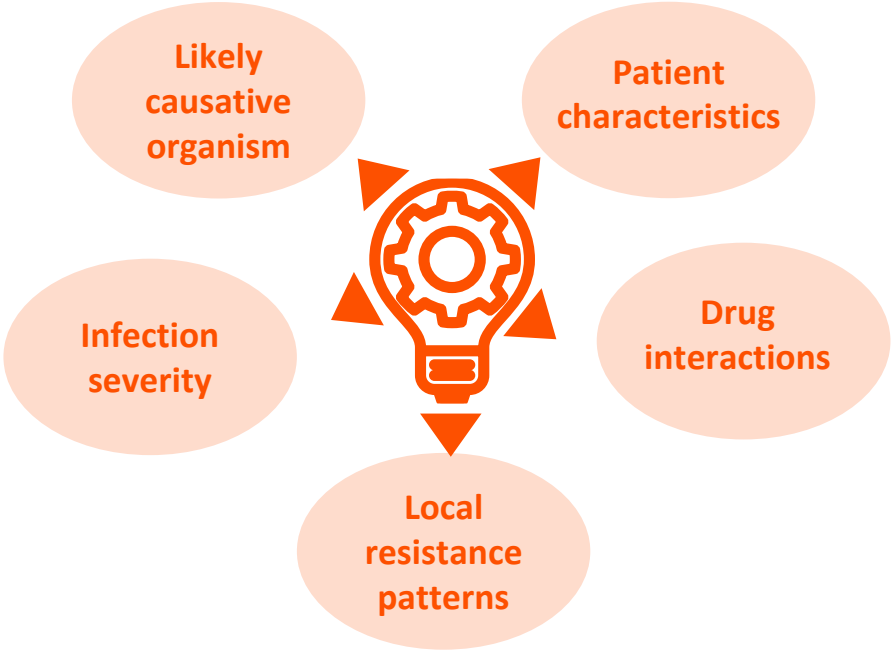
What criteria should clinicians use to select the most appropriate antimicrobial treatment?

Factors guiding antimicrobial treatment choice



Guidelines on common infections should be used as a reference by prescribers when choosing an antimicrobial therapy

Patel K, et al. *Cureus.* 2021;13:e13925.

When initiating antimicrobial treatment, what factors should be considered to ensure it is appropriate for the individual patient?

Timeline of antimicrobial therapy

Initiate of antibiotics

Early administration can reduce mortality and improve outcomes

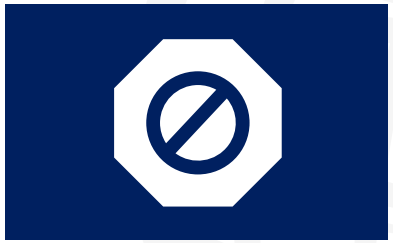
Determine course length

Often dependent on infection site, severity and causative organism

Continue, de-escalate or stop

- De-escalation based on culture results
- Elimination of redundant therapy can more effectively target causative pathogen

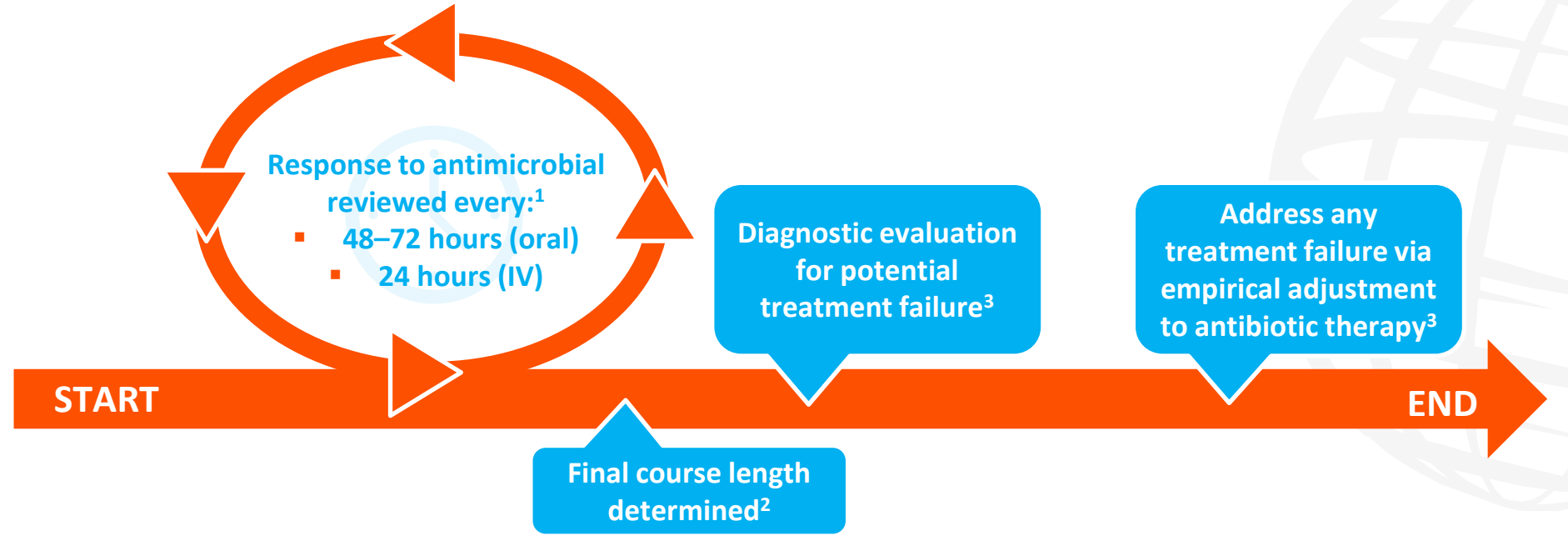
End of treatment



De Waele JJ, et al. *Intensive Care Med.* 2020;46:236–44.

How should patients receiving antimicrobial treatment be monitored?

Recommendations for monitoring patients receiving antimicrobial treatment



IV, intravenous.

1. Jethwa S. 2016. Available from https://pharmaceutical-journal.com/article/ld/principles-of-initiating-antimicrobial-therapy-and-empiric-prescribing (accessed 31 January 2022); 2. Public Health England. 2015. Available from: www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus (accessed 31 January 2022); 3. Bassetti M, et al. *Intensive Care Med.* 2018;44:73–5.

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New and emerging management options for antibiotic-resistant infections

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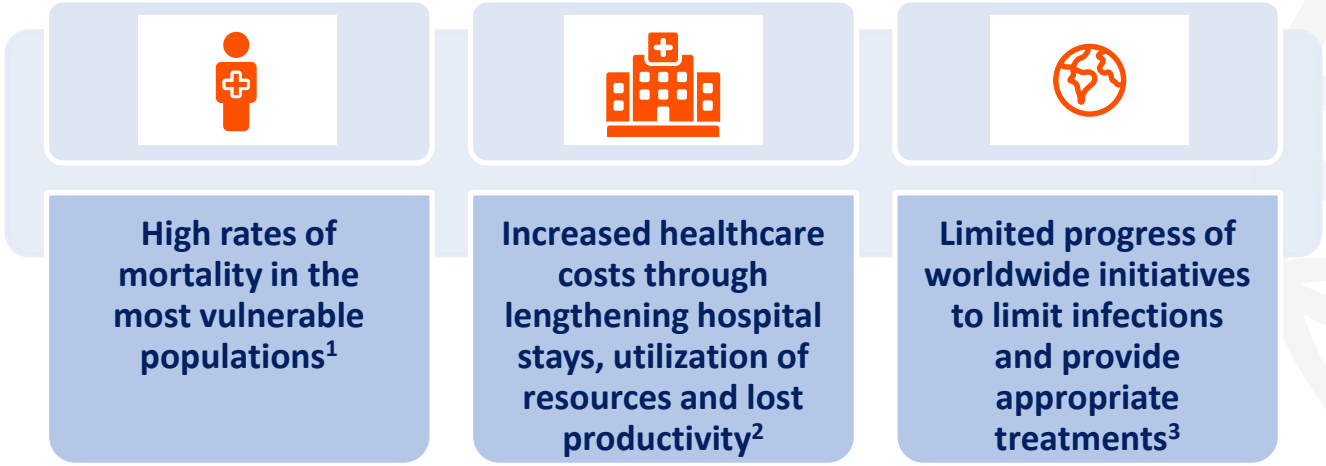
Why are new management options for antibiotic-resistant infections needed?

New management options are needed for multi- and extensively-drug resistant bacteria



Evidence-based AMS programmes help to address these challenges

AMS, antimicrobial stewardship.

1. Cassini A, et al. *Lancet Infect Dis.* 2019;19:56–66; 2. Naylor NR, et al. *Antimicrob Resist Infect Control.* 2018;25:58;
3. WHO 2019. Available from: www.who.int/docs/default-source/documents/no-time-to-wait-securing-the-future-from-drug-resistant-infections-en.pdfsfvrsn=5b424d7_6 (accessed 18 January 2022).

What data support the use of new non-β-lactamase inhibitor therapies for addressing antibiotic-resistant infections?

Non-β-lactamase inhibitors can be effective for the treatment of several types of infection

Plazomicin

- The phase III EPIC study in cUTIs, including acute pyelonephritis, reported plazomicin was noninferior to meropenem[1]
- The phase III CARE study in HABP/VABP reported fewer deaths from day 14 to day 60 with plazomicin-based combination therapy[2]

Eravacycline

- The phase III IGNITE1 and IGNITE4 studies in cIAIs reported eravacycline was noninferior to ertapenem and meropenem, respectively[3,4]
- Phase III trials of eravacycline vs ertapenem (NCT03032510) and levofloxacin (NCT01978938) for cUTI showed lower cure rates for eravacycline[5]

Murepavadin[6]

- The phase III PRISM-MDR and PRISM-UDR studies of IV murepavadin halted due to a higher than expected frequency of acute kidney injury
- Development of inhaled murepavadin continues including for *Pseudomonas aeruginosa* infections in people with cystic fibrosis

Colistin[7]

- Broad-spectrum activity against carbapenem-resistant pathogens
- Use is often limited because of nephrotoxicity
- Discrepancy exists between antimicrobial efficacy observed in laboratory testing vs clinical observation

cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; IV, intravenous; VABP, ventilator-associated bacterial pneumonia.

1. Wagenlehner FME, et al. *N Engl J Med*. 2019;380:729–40; 2. McKinnel JA, et al. *N Engl J Med*. 2019;380:791–3; 3. Solomkin J, et al. *JAMA Surg*. 2017;152:224–32; 4. Solomkin JS, et al. *Clin Infect Dis.* 2019;69:921–9; 5. Yusuf E, et al. *J Clin Med.* 2021;10:1068; 6. Provezani A, et al. *Int J Clin Pharm*. 2020;42:1016–25; 7. Doi Y. *Clin Infect Dis*. 2019;69(Suppl. 7):S565–75.

What is the potential role for β-lactamase inhibitors in treating antibiotic-resistant infections?

Combination therapy with β-lactamase inhibitors can help restore efficacy against MDR infections

cUTIs (including acute pyelonephritis)

Relebactam/imipenem/cilastatin:[1]

- Noninferior (at 250 mg and 125 mg relebactam) to imipenem/cilastatin, measured by microbiological response rates

Vaborbactam/meropenem:[2]

- Noninferior to piperacillin/tazobactam, measured by a composite outcome of complete resolution or improvement of symptoms

Avibactam/ceftazidime:[3]

- Similar to the best available therapy, measured by clinical cure at the test-of-cure visit

cIAIs

Relebactam/imipenem/cilastatin:[4]

- Noninferior (at 250 mg and 125 mg relebactam) to imipenem/cilastatin, measured by clinical response rates at DCIV

Avibactam/ceftazidime:[3]

- Clinical cure rate at the test-of-cure visit was higher with avibactam/ceftazidime vs best available therapy

cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; DCIV, discontinuation of intravenous therapy; MDR, multidrug resistant.

1. Sims M, et al. *J Antimicrob Chemother*. 2017;72:2616–26; 2. Kaye KS, et al. *JAMA*. 2018;319:788–9; 3. Carmeli Y, et al. *Lancet Infect Dis*. 2016;16:661–73;
4. Lucasti C, et al. *Antimicrob Agents Chemother*. 2016;60:6234–43.

Combination therapy with β-lactamase inhibitors can help restore efficacy against MDR infections

HAP and VAP

- **Tazobactam/ceftolozane:**[1]
  - Noninferior to meropenem, measured by all-cause mortality at 28 days
  - 25% of patients were infected with *Pseudomonas aeruginosa*
- **Avibactam/ceftazidime:**[2]
  - Noninferior to meropenem, measured by clinical cure at a test-of-cure visit
  - 30% of patients were infected with *Pseudomonas aeruginosa*
- **Relebactam/imipenem/cilastatin:**[3]
  - Noninferior to tazobactam/piperacillin, measured by day 28 all-cause mortality and favourable clinical response at early follow-up
  - 18.9% of patients were infected with *Pseudomonas aeruginosa*

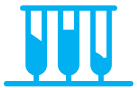
HAP, hospital-associated pneumonia; MDR, multidrug resistant; VAP, ventilator-associated pneumonia.

1. Kollef MH, et al. *Lancet Infect Dis*. 2019;19:1299–311; 2. Torres A, et al. *Lancet Infect Dis*. 2018;18:285–95; 3. Titov I, et al. *Clin Infect Dis*. 2021;73:e4539–48.

How can clinicians incorporate new and emerging therapies into their daily clinical practice?

Key factors for incorporating new and emerging therapies

Newer agents should be used within the context of AMR surveillance based on local epidemiology and the major clinical impact attributable to a specific AMR profile[1]



Fast, robust and affordable antimicrobial susceptibility testing methods are in development to decrease the time required[2]

To combat the development of resistance, newer antibiotics should not be used indiscriminately but targeted at patients with specific therapeutic requirements[3]

AMR, antimicrobial resistance.

1. Pezzani MD, et al. *J Antimicrob Chemother.* 2020;75:ii2–ii19; 2. Vasala A, et al. *Front Cell Infect Microbiol.* 2020;10:308; 3. Cars O, et al. *Lancet Glob Health.* 2021;9:e1022–7.

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