World Health Organization

Western Pacific Region

Strengthening Clinical Diagnostic Stewardship in the Western Pacific Region

A practical manual

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Strengthening clinical diagnostic stewardship in the Western Pacific Region: a practical manual

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FOREWORD

Antimicrobial resistance (AMR) is one of the most pressing health challenges of our time, putting lives, livelihoods and health systems at risk, and reversing decades of progress in global health. Antibiotic resistance is increasing globally, with one in six laboratory-confirmed bacterial infections worldwide resistant to treatment in 2023.

AMR threatens to undermine medical treatments, including routine surgeries, maternal and child health, and cancer care. In the World Health Organization (WHO) Western Pacific Region alone, projections estimate up to 5.2 million deaths and US$ 148 billion in excess costs due to drug-resistant bacterial infections between 2020 and 2030.

Combating AMR in the human health sector requires an integrated approach to optimizing detection, investigation and treatment of bacterial infections, complemented by measures to prevent and control transmission of infections.

Patient outcomes can be improved by accurate microbiological diagnosis and prompt treatment of infections with appropriate antimicrobials. Improved outcomes result in shorter hospital stays, lower mortality and reduced health-care costs.

Accurate microbiological diagnosis is only possible when the *right* diagnostic test is taken, from the *right* patient, at the *right* time, using the *right* specimen collection techniques and testing methodologies. Results must be interpreted, reported and communicated in the *right* way by the *right* people to optimize the quality of clinical care.

Strengthening Clinical Diagnostic Stewardship in the Western Pacific Region – A practical manual has been developed in collaboration with the three levels of WHO, as well as regional experts, to address gaps in the practice of clinical diagnostic stewardship recognized in many Member States in the Region.

The manual is intended for use by clinicians and other health-care professionals practising in low-resource settings, aiming to strengthen their understanding and practice of clinical diagnostic stewardship. Hospital administrators and policy-makers may also find the manual useful to institutionalize clinical diagnostic stewardship activities and capacity-building in health-care facilities.

Improvements in clinical diagnostic stewardship will save lives by promoting accurate and timely diagnosis, leading to better individual patient management and outcomes, better-quality AMR surveillance data and reductions in low-value health care.

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Regional Director for the Western Pacific
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ABBREVIATIONS

AMR	antimicrobial resistance
AMS	antimicrobial stewardship
AST	antimicrobial susceptibility testing
CFU	colony-forming units
CoNS	coagulase-negative staphylococci
CRBSI	catheter-related bloodstream infection
CSF	cerebrospinal fluid
ECG	electrocardiogram
ESBL	extended-spectrum beta lactamase
GLASS	Global Antimicrobial Resistance and Use Surveillance System
ICU	intensive care unit
IPC	infection prevention and control
IT	information technology
IV	intravenous
MRSA	methicillin-resistant *Staphylococcus aureus*
PCR	polymerase chain reaction
PICC	peripherally inserted central catheter
SOP	standard operating procedure
TB	tuberculosis
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
WHO	World Health Organization

GLOSSARY OF TERMS

Stewardship	
Clinical diagnostic stewardship (terminology as used in this document)	Promotes the clinical elements of diagnostic stewardship, focusing on requesting the *right* diagnostic test, from the *right* patient, at the *right* time, using the *right* specimen collection techniques; and testing the sample, and reporting, communicating, interpreting and acting on the results in the *right* way, to optimize the quality of clinical care. It also aims to reduce unnecessary resource utilization and health-care costs associated with inappropriate diagnostic testing and other aspects of low-value health care.
Diagnostic stewardship *(1, 2)*	Coordinated guidance and interventions to improve appropriate use of microbiological and other diagnostics to guide therapeutic decisions. It should promote appropriate, timely diagnostic testing; collection and identification of specimens; and accurate, timely reporting of results to guide patient treatment.
Antimicrobial stewardship (AMS) *(3)*	A coherent set of actions which promote the responsible use of antimicrobials. This definition can be applied to actions at the individual level as well as the national and global level, and across human health, animal health and the environment.
AMS principles	Principles guiding antimicrobial use to maximize clinical effectiveness while minimizing toxicity, unnecessary costs and antimicrobial resistance.
Antimicrobial spectrum of activity	The range of microorganisms that an antimicrobial can kill or inhibit the growth of.
Empiric antibiotic therapy *(4)*	Initial antibiotic treatment given before the specific pathogen causing an infection is identified through microbiological testing.
Targeted/definitive antibiotic therapy *(4)*	The antibiotic regimen selected for the specific pathogen after it has been identified and antimicrobial susceptibility testing (AST) has been completed and results are known. Antibiotic choices are guided by known microbiology results.
Concepts	
Cognitive bias *(5)*	A series of unconscious, systematic errors in thinking and interpreting, which leads to biased decision-making, with decisions based on beliefs or assumptions rather than facts.
Diagnostic error *(6)*	Failure to establish a correct and timely explanation of a patient's health problem, including delayed, incorrect or missed diagnoses, or a failure to communicate the diagnosis to the patient.

Laboratory testing	
Pre-analytical phase	Steps starting, in chronological order, from: i. the appropriateness of the request/test selection for a particular patient made by the clinician (sometimes referred to as the pre-pre-analytical phase); and ii. sample collection, handling and transportation to and within the laboratory.
Analytical phase	The diagnostic procedures, processes and products involved in testing samples that ultimately provide test results.
Post-analytical phase	Processes following the diagnostic testing of samples including systematic review, formatting and interpretation, authorization for release, reporting and communication of test results, and storage of samples of the examinations.
Microbiology reporting	
Cascade reporting	A form of selective reporting where antimicrobial susceptibility results for second-line antibacterial agents (usually broader spectrum) are only reported to clinicians if organisms are resistant to first-line agents. This promotes the use of narrower-spectrum antibiotics, when appropriate, without compromising patient outcomes.
Selective reporting	Reporting results of AST for specific antimicrobials only, based on defined criteria such as organism identification, body site, clinical setting or patient demographics. This promotes antimicrobial stewardship by guiding prescribers to choose optimal, narrow-spectrum and less toxic agents, and can decrease inappropriate and unnecessary antibiotic prescriptions.
Test characteristics	
False negative	A test result from a patient who *does* have the disease in question, but which incorrectly reports they do not.
False positive	A test result from a patient who *does not* have the disease in question, but which incorrectly reports they do.
Likelihood ratio *(6)*	The probability of a positive test in patients *with* the disease (sensitivity) divided by the probability of a positive test in patients *without* the disease (1 - specificity). This ratio can be used to estimate the probability of the disease in individual patients.
Negative predictive value *(7)*	The proportion of patients with a negative test result who truly *do not* have the outcome of interest. Answers the question: *"If I have a negative test, what is the probability that I don't have the disease?"*

Positive predictive value *(7)*	The proportion of patients with a positive test result who truly *do* have the outcome of interest. Answers the question: *"If I have a positive test, what is the probability that I actually have the disease?"*
Post-test probability *(6)*	The likelihood of a patient having a disease after a diagnostic test result is known.
Pre-test probability *(6)*	The likelihood of a patient having a disease before a diagnostic test result is known. The higher the pre-test probability, the more likely it is that a diagnostic test will further the diagnostic process.
Sensitivity	A test's ability to correctly identify those *with* a disease or outcome of interest (true positives).
Specificity	A test's ability to correctly identify those *without* the disease or outcome of interest (true negatives).
Tools	
Clinical algorithm	A written guide that presents a sequence of clinical decisions, often as a flow chart, to guide patient management for a clinical problem.
Clinical decision tool	Any tool that provides timely information, usually at the point of care, to help inform decision-making in the clinical workflow of a patient's care.
Standard operating procedure (SOP)	Written instructions for doing a specific task in a certain way.

Introduction

The World Health Organization (WHO) identifies antimicrobial resistance (AMR) as one of the top 10 global health threats. Alarming levels of bacterial resistance are being reported, with one in six laboratory-confirmed bacterial infections worldwide resistant to first-line treatment in 2023 *(8)*. This is resulting in common infections becoming more difficult to treat, and life-saving medical and surgical procedures becoming riskier to perform. In the WHO Western Pacific Region alone, infections with drug-resistant bacteria are projected to result in up to 5.2 million deaths and US$148 billion in excess economic costs between 2020 and 2030 *(9)*.

Optimizing use of diagnostic tests or "diagnostic stewardship" is critical for individual patient care, improving patient outcomes and reducing health-care costs *(10)*. While diagnostic stewardship traditionally focuses on microbiological testing, it is important to recognize that in clinical practice, biochemistry, other laboratory tests and imaging may also contribute to establishing or excluding a diagnosis. Inappropriate, under-use or overuse of diagnostic tests can lead to incorrect or delayed diagnoses and inappropriate treatment of patients, potentially leading to patient harm, prolonged hospital stays, unnecessary health-care costs and inefficient use of resources.

Microbiological testing of clinical specimens taken as part of routine clinical care also provides data that form the backbone of passive AMR surveillance. AMR surveillance data are used to monitor trends in AMR, detect AMR pathogen outbreaks, and inform antimicrobial stewardship (AMS) and other health policies.

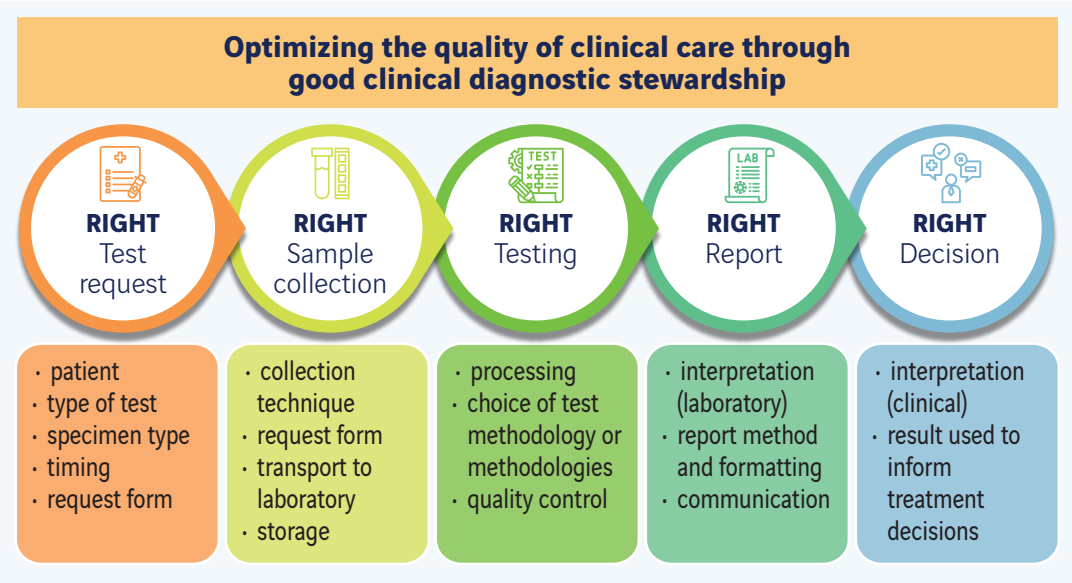
Clinical diagnostic stewardship

Clinical diagnostic stewardship promotes requesting the *right* diagnostic test, from the *right* patient, at the *right* time, using the *right* specimen collection technique; and testing the sample, and reporting, communicating, interpreting and acting on the results in the *right* way to optimize the quality of clinical care (Fig. 1). It also aims to reduce unnecessary resource utilization and health-care costs associated with inappropriate diagnostic testing and other aspects of low-value health care. Ideally, clinical diagnostic stewardship guidelines should align with a country's national essential diagnostic list, where available, to support procurement planning and ensure sustained availability of diagnostics.

This document takes a patient-centred approach to the day-to-day decisions and clinical practices carried out by clinicians and other frontline health-care workers (hereafter collectively referred to as clinicians) that contribute to clinical diagnostic stewardship. It focuses on bacteriological testing – microscopy, pathogen identification and antimicrobial susceptibility testing (AST) – as the mainstay of microbiological diagnosis of infectious disease. But it should be remembered that judicious use of serological and molecular testing – where available, for example, for respiratory viruses – can also play an important role in diagnosis.

Promoting and practising good clinical diagnostic stewardship requires sustained behaviour change. The Malaysian case study described in Section 1 highlights how changes can be made in clinical practice, but recognizes that interventions must be continuous or repeated and complemented by frequent feedback and reminders to be impactful.

Fig. 1. Clinical diagnostic stewardship



Source: WHO

Objectives of clinical diagnostic stewardship

1. The primary objective of clinical diagnostic stewardship is to enable accurate and timely diagnosis and improve individual patient management and outcomes by informing therapeutic decisions.

   Benefits include appropriate choice of antimicrobials and enhanced resource efficiency, and reductions in antimicrobial exposure, adverse drug events, lengths of hospital stay, mortality and the economic burden of low-value health care[1] *(3)*.

2. In addition, good clinical diagnostic stewardship improves the representativeness and quality of AMR surveillance data obtained from microbiological testing of routine clinical specimens. The data can be used to support the early detection of outbreaks and inform national and local treatment guidelines and AMR control strategies.

Target audience

This manual is primarily intended for clinicians and other health-care professionals including members of committees or teams practising in low-resource settings, aiming to strengthen their understanding and practice of clinical diagnostic stewardship (Box 1).

Box 1. Primary audience

- Clinicians and other frontline health-care professionals responsible for assessing patients, ordering tests, collecting specimens and taking actions based on the results of microbiological testing.
- Health-care professionals involved in AMR surveillance, AMS and infection control activities, including hospital epidemiologists/surveillance officers, infection control nurses, microbiology laboratory staff and pharmacists.

[1] Low-value health care includes, for example, taking wound swabs, sputum samples and urine cultures from people without symptoms of infection, unnecessary antibiotic prophylaxis and antibiotic treatment of viral infections.

Hospital administrators, policy-makers and educators (Box 2) may also find the manual useful to institutionalize clinical diagnostic stewardship activities and capacity-building in health-care facilities.

Box 2. Secondary audience

- Hospital administrators responsible for supporting clinical diagnostic stewardship initiatives, including funding and resource allocation.
- National policy-makers responsible for establishing and promoting national AMS programmes, including resource allocation and the development and implementation of health policies and guidelines.
- Educators and institutions, including professional societies, responsible for training health-care professionals in clinical diagnostic stewardship.

Overview of the manual

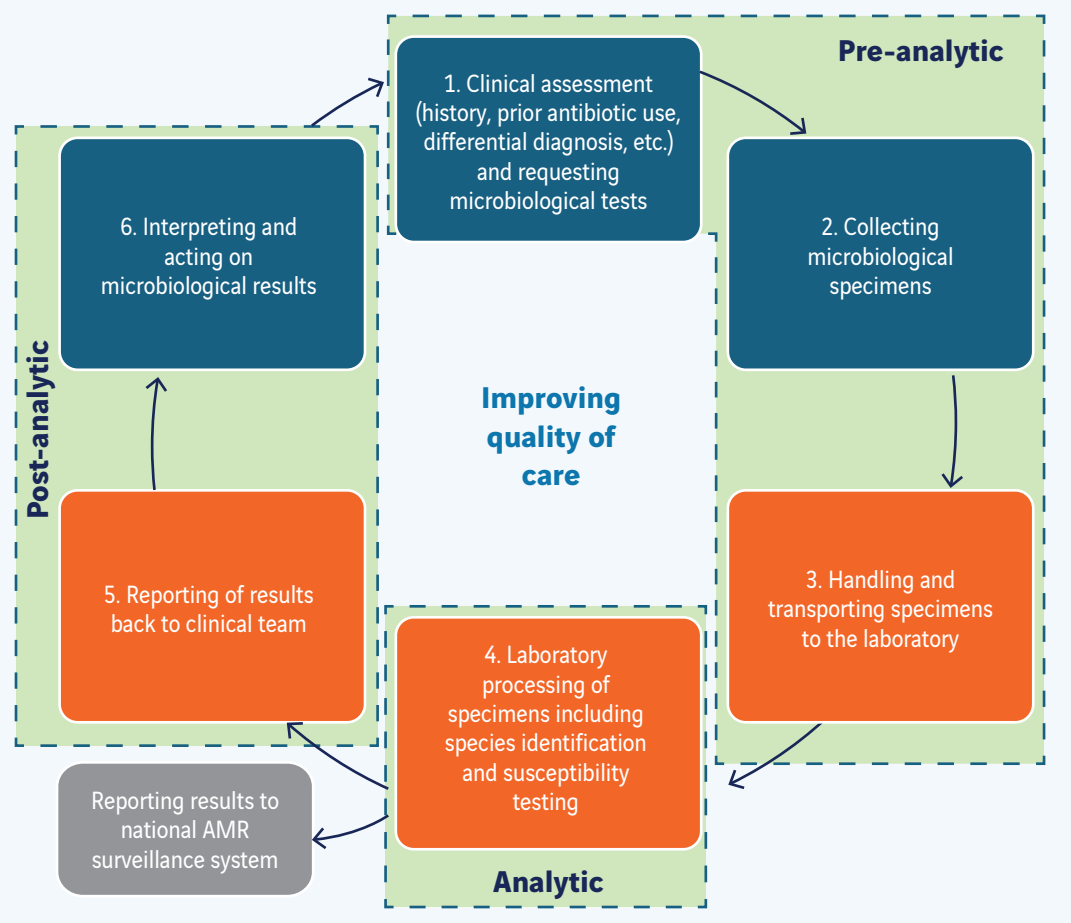
Section 1 of this manual describes the steps of clinical diagnostic stewardship, focusing on Steps 1, 2 and 6, which generally fall under the responsibility of clinicians, highlighting common barriers and the use and accuracy of diagnostic tests. Section 2 describes the importance of monitoring and evaluation of clinical diagnostic stewardship activities as part of quality-assurance mechanisms. Section 3 summarizes the role of the microbiology laboratory in clinical diagnostic stewardship practices. Section 4 links clinical diagnostic stewardship to AMS and infection prevention and control (IPC) activities and Section 5 describes the support needed from different stakeholders to promote sustainable clinical diagnostic stewardship practices. Section 6 presents examples of clinical diagnostic stewardship activities as clinical case studies from countries in the Western Pacific Region.

1. The diagnostic stewardship pathway

The diagnostic stewardship pathway consists of six key steps (Fig. 2), conventionally divided into pre-analytic, analytic and post-analytic phases. The accuracy, reliability and utility of diagnostic tests are dependent on good clinical diagnostic stewardship practices at all stages of the pathway.

Good diagnostic stewardship aims to address both under-testing and over-testing. In resource-limited settings, the former can be addressed by focusing on patients with severe infections such as a bloodstream infection/suspected sepsis, or on infections and pathogens of public health importance in the country. Over-testing can be reduced, for example, by carefully considering whether taking wound, sputum or urine samples from patients without symptoms of infection is necessary.

Fig. 2. The diagnostic stewardship pathway



Source: WHO

Steps 1, 2 and 6 (Fig. 2, blue boxes) represent the clinical components of the diagnostic pathway, in which clinicians, microbiology staff and support staff play a central role, and which are the focus of this document.

Steps 1, 2 and 3 together form the "pre-analytic" phase of microbiological testing. This is the leading source of error in laboratory diagnostics, responsible for an estimated 60–70% of all laboratory errors *(11)*. These errors, including inappropriate test requests, specimen collection mishandling, specimen mislabelling/misidentification and transportation delays, directly compromise the accuracy and utility of results and the quality of patient care.

Step 1. Clinical assessment and ordering microbiological tests

A physical examination is an important part of a clinical assessment for diagnosing illness and deciding which tests are needed.

When a patient presents with signs or symptoms suggestive of an infection, it is important that the clinician conducts a thorough history and examination, and critically considers the differential diagnosis, to decide which microbiological tests, if any, will help establish the correct diagnosis, which may include non-infective conditions. This process demands judicious test selection, guided by the patient's clinical presentation, relevant risk factors including history of prior antibiotic use and/or hospitalization, and knowledge of local disease epidemiology.

Box 3 summarizes foundational knowledge clinicians need to support decision-making, reduce cognitive bias and ensure that the *right* specimens reach the laboratory at the *right* time and in the *right* condition, avoiding over-testing as well as under-testing. If unsure, clinicians should consult a senior clinician, a microbiology staff member or a clinical microbiologist, as appropriate.

Microbiological tests are not always necessary. When requesting a test, the clinician should carefully consider whether receiving a positive or negative test result will lead to a change in clinical management of the patient – the pre-test probability of the test. If the test result will not alter the management in a timely manner, it may not be needed. The first step is to decide whether microbiological test(s) are needed and then ensure that the *right* test is selected for the *right* patient.

Box 3. Foundational knowledge for clinical diagnostic stewardship

Understanding the basic principles of clinical diagnostic stewardship enables clinicians to critically assess diagnostic tests and make informed decisions about patient management. See the Glossary for definitions of the terms.

Clinicians should understand:

- The **sensitivity** and **specificity** of different tests, noting that:
  - tests with high sensitivity are used for screening to capture as many cases as possible (true positives);
  - tests with high specificity are used to ensure that patients without the disease are not included (true negatives); and
  - sensitivity and specificity are intrinsic to the test itself and are not affected by disease prevalence or other population characteristics.
- How the local context, including disease prevalence, influences **positive predictive values**, **negative predictive values** and **pre-test probability**, noting that:
  - the **positive predictive value** is higher if the disease prevalence is high – if the disease is common, a positive test is likely to be a true positive; if a disease is rare, a positive test result may be a false positive;
  - the negative predictive value is higher when the disease prevalence is low – if the disease is common, a negative test result may be a false negative; if the disease is rare, a negative test result is likely to be a true negative; and
  - the pre-test probability is related to the prevalence of the disease in the population and patient risk factors, such as age and symptoms.
- The risk of **false positive** and **false negative results** and **cognitive bias**, noting that:
  - false positive results are more likely if a disease is rare;
  - false negative results are more likely if a disease is common; and
  - cognitive bias can lead to clinicians disregarding test results that do not fit with their initial diagnosis or only taking account of information that confirms their pre-existing impression or belief.

Things to consider when deciding on which diagnostic tests to order:

- What is the most likely diagnosis?
- What other possible explanations are there for the patient's presentation and how likely are they?
- Have previous test results been reviewed?
- What test(s) will help confirm/exclude a diagnosis, what is the turnaround time and how will the results of the test(s) influence the clinical management of this patient?
- Is the test available and accessible in the hospital and can the patient afford to pay for it (if relevant)?
- Is the test appropriate for this patient? Is there the necessary expertise to perform the test? Should this test be ordered at all?
- Is there any risk of harm from performing this test, including the possibility of false negative or false positive results?
- Is an expert opinion needed?
- Do all tests need to be requested now? or:
  - Can appropriate clinical samples for microbiology testing be collected before starting empiric antibiotic therapy?
  - Can tests be requested sequentially, informed by the results of initial tests?

USE OF CLINICAL DECISION TOOLS

Simple tools, such as prompting questions or a clinical algorithm, can support clinical decision-making by helping clinicians to evaluate patients correctly and consistently by asking the right questions during the clinical assessment and to order appropriate diagnostic tests, not only microbiological tests but also other laboratory tests and imaging studies.

Clinical decision tools are checklists or sets of questions that support clinicians to follow evidence-based processes. Most often these are paper-based or available on a device.[2]

COMMON PROBLEMS ENCOUNTERED AT STEP 1

- **Under-testing** – not requesting tests when they are clinically indicated, for example, from patients with suspected sepsis and other severely ill patients, or collecting blood cultures only for patients failing antibiotic therapy or deteriorating clinically.
- **Inappropriate test request** – requesting tests that are not aligned with the clinical presentation, or which may not help to make a diagnosis or influence the management of the patient. Examples of microbiological over-testing include routinely sending:
    - wound swabs from chronic ulcers with no clinical signs of infection;
    - sputum samples from patients with respiratory symptoms:
        - unless the patient is an adult with moderate to severe respiratory disease or who is immunocompromised;
        - unless the sputum sample is being taken to confirm or exclude a diagnosis of tuberculosis (TB); and
        - as sputum samples cannot be obtained from young children (below the age of 10 years) unless the child is intubated,

      noting that problems arise as sputum samples of patients with respiratory symptoms are often of poor quality, thus objective assessment of sputum quality to guide decisions on further testing or interpretation of results is suggested;
    - catheter urine samples from asymptomatic patients;
    - central venous catheter tips after extraction from asymptomatic patients; and
    - non-diarrhoeal stool samples for *Clostridioides difficile* testing.
- **Over-requesting tests** (pan-culturing) – requesting and/or repeating a barrage of tests without careful consideration of the patient's symptoms or clinical status and what diagnosis is most likely. Frequently there is time for additional tests, such as serology tests, to be considered and requested if still deemed necessary after the results of initial culture-based tests are known.
- **Barriers to testing** – leading to delays in collecting clinical samples or tests not being requested or performed at all, including:
    - cost of testing for the patient or the hospital;
    - non-inclusion of microbiological tests in health insurance packages;
    - lack of availability of tests, reagents and other consumables;
    - limited numbers of staff available to collect and test clinical samples; and
    - diagnostic uncertainty and risk tolerance – tests may not be ordered if the clinician is not confident about the diagnosis or if the possible severity of the presentation is not

[2] If available, more advanced clinical decision tools, integrated into electronic health records, can provide real-time decision-making support for appropriate diagnostic testing. These systems may incorporate automated alerts about the appropriateness of a certain test or suggest alternatives based on available information; alerts may be triggered if a clinician attempts to order a duplicative test or a test without sufficient clinical justification. Alternatively, clinicians may be prompted to request, for example, blood cultures for a patient with suspected sepsis.

recognized, for example, in cases of suspected sepsis, paediatric patients and febrile illness in low-resource settings.

- **Incorrect specimen type or collection site** – requesting the wrong specimen type, sampling the wrong anatomical site or not specifying the specimen type or collection site. If in doubt about the correct testing strategy, consult with the microbiology staff first.
- **Incorrect or incomplete test request form** – including inaccurate information or omitting demographic and clinical information, such as age, sex, diagnosis, relevant past medical history and antimicrobial history, which may guide the microbiologist in determining which tests to run.

ROLE OF HOSPITAL MANAGEMENT

Clinical care can be improved when standardized, user-friendly and up-to-date clinical decision tools are developed and are accessible at the point-of-care and integrated into routine clinical workflows. Tools should include recommendations tailored to the most likely and/or most important initial tests, with guidance as to when more intensive testing is warranted. Hospital management should actively support the development, implementation and continuous improvement of tools by providing the necessary infrastructure, training and resources.

Step 2. Collecting microbiological specimens

Proper specimen collection and testing techniques are vital to ensuring accurate and reliable results.

Once a diagnostic test has been requested, the next step is to collect the specimen at the *right* time using the *right* specimen collection technique (Fig. 1) and ensure the request form is completed correctly. Timing of specimen collection can significantly impact the accuracy and reliability of the test results. For example, to reduce the chance of a false negative result, blood cultures should be collected before antibiotics are given to the patient when possible, avoiding any delay in antibiotic administration when the patient is severely ill.

Specimen contamination with skin or other microbiota is a common problem which reduces the value of microbiological testing, most importantly for blood cultures and samples taken from other sterile sites. Contamination can take place anywhere along the diagnostic pathway, but most commonly occurs due to poor aseptic technique during specimen collection. These contaminated results can have a major impact. They consume considerable human resources (time and effort) and laboratory consumables.

Responsible staff must be properly trained in correct specimen collection techniques to minimize contamination of samples and risk of harm to patients.

Microbiological specimens may be collected by clinicians, nurses, phlebotomists or allied health workers, who are trained and competent in adhering to specimen collection standard operating procedures (SOPs) to prevent contamination and ensure that specimens are representative of the infection site.

Samples may also be self-collected by patients. For samples collected by the patient, for example, mid-stream urine samples, clear verbal or written instructions should be given on how to collect the sample to minimize the risk of contamination.

SPECIMEN COLLECTION SOPS

SOPs promote standardized best practices for microbiological specimen collection by providing step-by-step guidance. If followed correctly and consistently, SOPs support the collection of high-quality specimens, reducing the risk of contamination and improving diagnostic accuracy.

COMMON PROBLEMS ENCOUNTERED AT STEP 2

- **Delayed or inappropriate timing of specimen collection** – if antimicrobials are given to the patient before, for example, blood cultures are collected, the likelihood of isolating a pathogen is reduced, which may lead to misdiagnosis and inappropriate treatment. However, sampling should not delay treatment of serious infections such as sepsis or meningitis.
- **Collecting the specimen from the wrong site** – for example, taking a blood culture from an existing intravascular line (peripheral or central line) rather than through peripheral venepuncture increases the risk of contamination. Drawing blood from an existing intravascular device may be considered when collecting blood from patients who fear needles to minimize pain (local anaesthetic creams are a possible alternative) or when culture from a central line is paired with a peripheral culture to detect central line-associated bloodstream infections. Strict adherence to aseptic technique must always be maintained.
- **Poor aseptic technique** – adhering to aseptic techniques to avoid contamination is particularly important when obtaining specimens from normally sterile sites (Boxes 4 and 5). This includes poor preparation or storage of locally produced disinfectant-soaked cotton balls (to avoid loss of efficacy due to evaporation), or using poor-quality, over-diluted or contaminated disinfectant solutions.
- **Incorrect sample volume** – inadequate specimen volume or quantity significantly reduces the likelihood of isolating a pathogen, leading to poor-quality results and misdiagnosis or delayed diagnosis. Overfilling blood culture bottles dilutes the culture medium and increases the risk of false positive results.
- **Using the wrong container or media** – will lead to specimen rejection and the need to obtain a repeat sample with risks of harm to the patient and delays in processing and generation of results. Processing of the original sample could lead to inaccurate results and misinterpretation as different specimen types require specific conditions or media.
- **Delay in transporting the specimen to the laboratory or incorrect storage pending transport** – including storing the specimen at the wrong temperature, which can lead to decreased culture positivity rates, or in the case of urine samples, bacterial proliferation, making results difficult to interpret.
- **Unlabelled or incorrectly labelled specimen** – failure to accurately label specimens with patient identification information[3] and the date and time of collection may result in specimen misidentification, rejection or delays in processing by the laboratory.

[3] Patient details should include at least three pieces of identification information, for example, name, date of birth and unique identification number.

Box 4. Malaysia case study

Reducing blood culture contamination rates using a multimodal intervention – adapted from a presentation given by Dr Sahlawati Mustakim, Hospital Sungai Buloh, Malaysia, for the webinar "Strengthening antimicrobial stewardship. Strategies and best practices from across the Western Pacific Region" held on 21 November 2024.

Problem: Blood culture contamination is a critical issue because it can lead to misdiagnosis and inappropriate treatment. Every positive blood culture must be taken seriously. Reducing contamination rates ensures the accuracy and reliability of results.

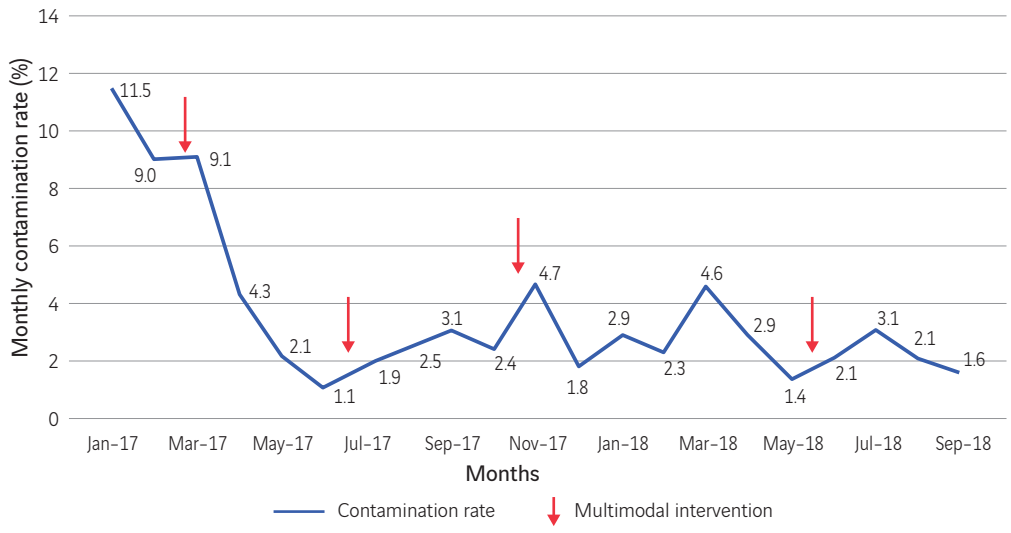
Evidence

A Malaysian study (data from 2018)[a] found a blood culture contamination rate of 3.2% with a 12.5% blood culture positivity rate. Coagulase-negative Staphylococcus were the most frequent (71%) contaminants.

Multimodal intervention to address the problem[b]

- **Build it** – systems change, blood culture packs and daily stockkeeping
- **Teach it** – systematic training and education of relevant health-care workers
- **Check it** – monitoring of contamination rates and feedback to staff
- **Sell it** – reminders, continued communication and hand hygiene audits
- **Live it** – culture change led by senior staff providing a supportive environment.

Impact on monthly contamination rates in one hospital emergency department – January 2017 – September 2018



Source: Ministry of Health, Malaysia. Used with permission.

Take-home messages/lessons learnt

- Blood culture contamination rates are a serious concern that risk compromising patient outcomes and patient safety.
- It is possible to make changes and improve the use of scarce resources, but a one-time intervention is insufficient – efforts must be continuous with frequent feedback and reminders.

[a] Mokhtar *et al.* (2024) *(12).*
[b] WHO multimodal improvement strategy *(13).*

ROLE OF HOSPITAL MANAGEMENT

Awareness of the importance of clinical diagnostic stewardship among hospital leaders is critical to obtain buy-in and prioritize support for interventions. For example, hospital management can ensure that SOPs relating to microbiological specimen collection developed by the microbiology laboratory are made available and readily accessible to all health professionals. These products need to be regularly reviewed and updated based on the latest evidence, aligned with clinical workflows and included into regular training activities.

By embedding an awareness of the importance of proper specimen collection procedures in a culture of quality and safety, where leaders show that they care about the problem and are engaged in improvement initiatives, much can be done to minimize contamination.

Interventions include staff education and training to build awareness, skills and knowledge about the problem and how to minimize it, backed by the regular demonstration of competency on specimen collection techniques, regular monitoring of aseptic techniques and hand hygiene, and ongoing monitoring of contamination rates of blood cultures with near real-time feedback to wards.

Box 5. Reducing contamination of specimens from sterile sites

When collecting specimens from sterile sites – areas of the body normally free from microorganisms – it is crucial to adhere to strict aseptic techniques. Failure to do so can lead to contamination, often from skin flora, resulting in false positive results that can compromise patient care.

Sterile sites include but are not limited to:

- blood
- cerebrospinal fluid (CSF)
- pleural fluid
- peritoneal fluid
- pericardial fluid
- joint fluid
- bone marrow.

Non-sterile sites: Skin, urine and sputum are not sterile sites. The presence of bacteria in samples taken from skin wounds, urine and sputum may represent normal flora or colonization and not active infection.

It is important to promote hand hygiene for all patient care, regardless of the body site.

Step 6. Interpreting and acting on microbiological results

Good communication among clinicians, microbiologists and other health professionals is vital for interpreting microbiological findings correctly and guiding appropriate patient care.

Once microbiological test results have been reported by the laboratory, clinicians must: 1) interpret the findings; and 2) take the right actions based on the results. Decisions must also take into account the results of other tests and imaging studies.

Appropriate interpretation of microbiological results and subsequent actions require collaborative input from microbiology, combined with clinical judgement grounded in AMS principles. Infectious disease or other specialist consultation may be needed for complex cases.

Management decisions may involve altering antimicrobial therapy, through interventions that follow good AMS practices, such as escalation, de-escalation, discontinuation or dose/route of administration – intravenous (IV) to oral switch/duration adjustments – based on the clinical context. Factors to consider include the type of infection, adherence, gastrointestinal absorption, antimicrobial bioavailability and drug penetration to the site of infection. Oral therapy can reduce costs and avoid line-associated local or bloodstream infections. Systems-level considerations include antimicrobial availability and cost.

PATIENT-CENTRED INTERPRETATION OF RESULTS

Microbiological results should not be interpreted in isolation but should be considered together with the patient's complete clinical picture, the local epidemiology, and the results of other tests and imaging studies, when appropriate. Prompt questions can be helpful when evaluating the results:

- Does the result (for example, isolated organism) correlate with the clinical presentation?
- Is the organism typically associated with infections at this site, or could it represent contamination or colonization?
- Could there be another explanation for the patient's presentation, such as a non-infective cause?

If the results indicate an unusual or multidrug-resistant organism or an organism that is part of an outbreak, microbiologists, infectious disease and/or IPC specialists should be consulted in a timely manner to guide further actions that may be needed, for example:

- enhancing IPC measures
- reassessing the patient's clinical condition
- requesting additional investigations or tests
- altering treatment
- reporting the finding to the hospital management and/or AMR committee.

COMMON PROBLEMS ENCOUNTERED AT STEP 6

- **Distinguishing between clinically significant infection, colonization and specimen contamination** – requires critical interpretation of microbiology results in the context of the patient's presentation, physical findings and specific risk factors, for example, the number of blood culture bottles in which a possible contaminant is found. Not all isolates are clinically relevant, and the assumption that every identified organism requires treatment is a common diagnostic pitfall that directly drives unnecessary and inappropriate antimicrobial use (Box 6) *(14)*.
- **Failure to take into account ancillary test results**, such as whether white blood cells/polymorphs are found in a urine sample, or using the results of Gram staining, for example, visualizing numerous polymorphonuclear leukocytes and intracellular organisms to support the diagnosis of active infection.
- **Inappropriate prescribing or follow-up plan** – antibiotic therapy should be regularly reviewed to avoid continuing empiric broad-spectrum antibiotics without considering options to de-escalate or stop antibiotics. Negative microbiological results, interpreted in the context of the patient's clinical course and previous antibiotic therapy, can be helpful to encourage review of antibiotic treatment plans.
- **Failure to seek expert advice** – clinicians often fail to seek (or delay seeking) expert advice from specialists, such as microbiologists or infectious disease specialists for complex cases. If such expertise is not available, case discussion with peers can, nevertheless, be helpful.

Box 6. Common skin commensals typically considered as blood culture contaminants

- Coagulase-negative staphylococci (CoNS)
- *Cutibacterium acnes*
- Corynebacterium species
- Bacillus species (excluding *Bacillus anthracis*)
- Micrococcus species.

Isolation of skin commensals from only one of multiple blood culture sets collected for the same clinical episode generally supports a contamination event.

2. Monitoring, evaluation and feedback for quality assurance and improvement

Monitoring and feedback to clinicians and other stakeholders are important to ensure that clinical diagnostic stewardship activities form part of patient safety and quality-of-care mechanisms *(15, 16)*.

Ideally, indicators should evaluate both implementation (process indicators) and outcomes of activities, including measures of clinical outcomes and any unintended harm (Table 1). Disaggregating data by, for example, age, gender or geographical disparities, allows gaps or inequities in clinical diagnostic stewardship activities to be evaluated. Indicators can be discussed and adopted by the hospital body responsible for quality assurance, continuous quality improvement and patient safety and, for example, included among key performance indicators for relevant hospital staff.

Feedback of monitoring and results to staff can form part of individualized or case-based evaluations or as routine aggregated reports disseminated to staff or presented at meetings. Results can be compared against benchmarks (either individually, by ward/department or by facility), or through alternative feedback channels such as competitions. To maximize impact, feedback should be linked to action.

Table 1. Indicators to consider for monitoring clinical diagnostic stewardship activities

Step of the clinical diagnostic pathway	Examples of possible indicators
Step 1. Clinical assessment and ordering microbiological tests	• Percentage of tests ordered appropriately (for example, tests that meet defined criteria in line with clinical support tools), such as the percentage of patients presenting with suspected sepsis who had blood cultures taken.
Step 2. Collecting microbiological specimens	• Proportion of samples taken appropriately (for example, patients with suspected sepsis who had blood cultures *taken before starting antimicrobials*) • Proportion of adult patients from whom blood cultures were taken, that had *the correct number of bottles* taken as per facility SOP • Blood culture contamination rates • Blood culture positivity rates • Number of haemolysed specimens • Number of specimens with illegible or missing paperwork or labelling • Number of specimens that could not be processed due to incorrect sample volumes • Number and rates of sharps exposures/occupational injuries • Number (and percentage) of phlebotomy sessions where essential equipment was not available *(17)*.
Step 6. Interpreting and acting on microbiological results	• Time to reporting the Gram stain result from the time of a blood culture flagging positive • Time to identification of organism (by organism), from the time of a blood culture flagging positive • Percentage of patients who received appropriate antimicrobial therapy after critical results were reported back to clinical teams (for example, *Staphylococcus aureus* bacteraemia) • Number of consultations with specialists for complex or unusual results.

3. The role of the microbiology laboratory

Microbiologists are a key resource in ensuring that all steps in diagnostic stewardship pathways are appropriately implemented.

The microbiology laboratory plays a central role in Steps 3, 4 and 5 of the diagnostic stewardship pathway, but it contributes to all the other steps and is, therefore, vital to supporting clinical diagnostic stewardship overall (Table 2). The ability of the microbiology laboratory to contribute optimally to diagnostic stewardship depends on its resources (funding, staffing, infrastructure, etc.) and laboratory quality management, including external quality assurance.

Microbiologists are an important resource for educating and training clinicians on all aspects of clinical diagnostic stewardship including test characteristics and availability, choosing appropriate diagnostic tests, specimen collection and transport to the laboratory, and interpretation of results.

The microbiology laboratory is usually responsible for entering, validating and compiling microbiological data that are sent to the central level as part of national and regional AMR surveillance *(18)* and for submission to the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) *(19)*.

Table 2. Role of the microbiology laboratory in diagnostic stewardship

Step of the diagnostic stewardship pathway	Activities	Support to clinicians
Step 1. Clinical assessment and ordering microbiological tests	Set indications and criteria for diagnostic testing in collaboration with clinical departments – considering the test value and the cost and labour involved.	For example, culture will not be undertaken on fluids collected from drain bags, and urine culture will not be undertaken from bag specimens.
	Update hospital management on what diagnostic tests should be available.	Provide information on diagnostic test characteristics and their value and limitations.
	Support development and updating of clinical diagnostic tools.	Provide advice and training on appropriate selection of diagnostic tests based on clinical information.

Step of the diagnostic stewardship pathway	Activities	Support to clinicians
Step 2. Collecting microbiological specimens	Develop and update SOPs for specimen collection and evaluation of quality.	Provide advice and training on correct techniques and equipment, timing of specimen collection, preferred specimen collection site and specimen type, volume or quantity. Determine appropriate collection device or media and whether sample is suitable for further processing.
Step 3. Handling and transporting specimens to the laboratory	Develop and update SOPs on the proper handling, transportation and storage of specimens. Define and enforce specimen rejection criteria.	Provide advice and training on correct procedures. Provide feedback to health-care workers if a specimen is rejected (for example, improperly labelled specimen, poor quality, inadequate specimen volume or specimen transported or stored inappropriately).
Step 4. Laboratory processing of specimens including species identification and AST	Follow standardized protocols and ensure quality control for all tests undertaken in the laboratory, including species identification and AST. Ensure verification or validation of all assays offered and meet standards for ongoing quality assurance activities, including local accreditation standards.	Provide clinicians with accurate, reliable and timely microbiological results.
Step 5. Reporting results back to clinical teams	Review of test results and regular monitoring.	Alert clinical teams of results including the immediate notification of critical test results, such as preliminary blood culture results, or detection of multidrug-resistant organisms.
	Cascade or selective reporting of antimicrobial susceptibilities to support good AMS practices.	Support AMS efforts by promoting the appropriate use of antimicrobials and prescribing first-line narrow-spectrum antimicrobials over broader-spectrum or reserve antimicrobials (through cascade reporting), or, for example, only reporting nitrofurantoin on urine isolates because it is only used for treating uncomplicated urinary tract infections (UTIs) (selective reporting).
	Omit results that are not clinically relevant, for example, excluding sensitivities for likely contaminants.	Provide advice on differentiating between clinically significant pathogens and likely contaminants, for example, CoNS isolated from a blood culture.

Step of the diagnostic stewardship pathway	Activities	Support to clinicians
Step 6. Interpreting and acting on microbiological results	Provide advice to clinicians on the appropriate interpretation of test results.	Provide training and/or expert advice on appropriate empiric and targeted antimicrobial treatment options.
	Develop local antibiograms if the quality and quantity of local data allow.	Report antibiograms to hospital management to inform policy – such as antibiotic guidelines, AMS interventions, and/or allocation of resources for diagnostics and IPC.

Other areas	Activities	Support to clinical teams
Monitoring and evaluation of clinical diagnostic stewardship activities	Tracking indicators to monitor the implementation and outcome of clinical diagnostic stewardship activities in collaboration with clinicians and other teams.	Feedback to clinical teams on the implementation and effectiveness of clinical diagnostic stewardship activities. Identify good practices and areas for improvement.
Support AMR surveillance	Contribute to local and national AMR surveillance and GLASS by reporting data on pathogen prevalence and resistance trends to the national level.	Report surveillance data and provide guidance in using microbiological data to support clinical practice and development of policy.
Support outbreak investigations and response, including AMR-related outbreaks	Monitor unusual or increasing trends of pathogens and alarming resistance-patterns and mechanisms to trigger early investigation of potential outbreaks.	Inform IPC teams, clinical teams and relevant public health authorities of potential outbreak alerts, including AMR outbreaks, so that appropriate actions can be taken.

4. Linking clinical diagnostic stewardship with AMS and IPC

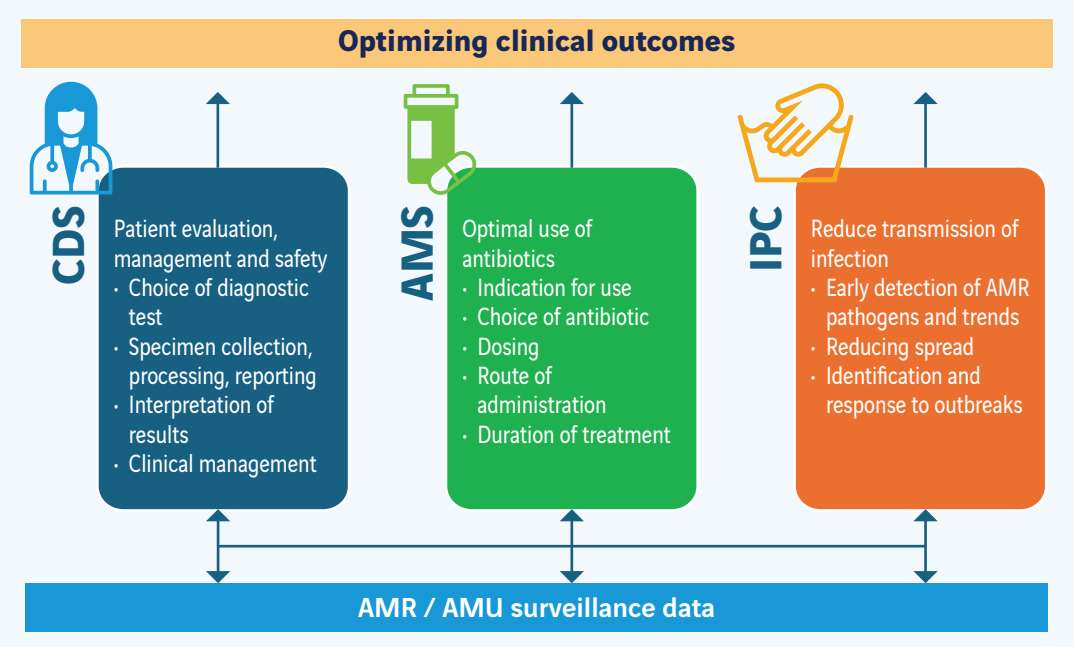
AMR control depends on activities conducted and coordinated at the patient, facility and policy level. Effectively managing patients with infectious diseases relies on coordinated diagnostic stewardship, clinical management, AMS and IPC, supported by AMR and antimicrobial use surveillance data. For example:

- AMR data are used to inform and evaluate AMS activities and implementation of IPC measures;
- cascade reporting supports narrow-spectrum antibiotic selection;
- rapid turnaround of AST shortens duration of empirical therapy and ensures appropriate targeted therapy;
- appropriate reporting formats support the interpretation of colonization rather than infection and reduce antibiotic therapy when no infection is present; and
- use of respiratory viral polymerase chain reaction (PCR) in patients with symptoms can identify infections that do not require antibiotics.

These areas are interconnected and interdependent and all need to be strengthened to improve patient management, safety and clinical outcomes, and mitigate the emergence and spread of infectious pathogens, including AMR pathogens (Fig. 3).

Successful implementation of these integrated areas of action depends on strong and accountable governance and technical leadership (for example, hospital management, relevant committees and senior clinicians), hospital policies, guidelines and SOPs, well-trained staff and continuous professional development activities.

Fig. 3. The bigger picture – optimizing clinical outcomes through clinical diagnostic stewardship, AMS, IPC and surveillance



AMR: antimicrobial resistance; AMS: antimicrobial stewardship; AMU: antimicrobial use; CDS: clinical diagnostic stewardship; IPC: infection prevention and control.

Source: WHO

5. Strong leadership and sustained commitment

Strong leadership and sustained commitment can strengthen clinical diagnostic stewardship, which can help can build stronger health systems and promote better health outcomes.

Effective leadership, governance and strong commitment at the national, regional and health-facility level are critical to fostering an environment that promotes successful implementation of measures to reduce AMR, including clinical diagnostic stewardship. Key features include strategic direction, accountability and cultivating an environment in which good clinical practices become embedded in individual practice and in the overall organizational culture. Collaboration and shared commitment enhance quality of care and patient safety, which benefits both patients and the health-care system.

The factors listed under the following four subheadings need to be considered in promoting strong leadership and sustained commitment:

GOVERNANCE AND LEADERSHIP – HEALTH FINANCING AND SYSTEMS STRENGTHENING

- Health financing structures at the national and facility level that promote optimal patient outcomes and equitable access to appropriate care, diagnostics and medicines, minimizing out-of-pocket costs for patients, ensuring equitable health insurance coverage.
- Dedicated funding for establishing systems and maintaining activities – including for infrastructure, education and training, and procurement and supply mechanisms.
- Supporting necessary infrastructure, including information technology (IT) infrastructure to support data management and analysis.
- Setting national standards, integrating clinical diagnostic stewardship into health-care policies and education curricula.
- Procurement processes/structures that ensure quality-assured consumables needed for testing and medicines needed for treatment are readily and consistently available.

POLICY AND GUIDELINES/CLINICAL GUIDANCE DOCUMENTS

- Develop policy and guidance documents that are aligned with broader health initiatives such as *The WHO AWaRe (Access, Watch and Reserve) antibiotic book (2)* and relevant WHO guidelines. These should be kept up to date with the latest evidence and integrated into hospital training, as well as clinical and operational workflows, including those embedded in national AMS, IPC, and compliance-monitoring and patient quality and safety programmes.

ENSURING A SKILLED AND COMPETENT WORKFORCE THROUGH EDUCATION AND TRAINING

- Hospital leadership and medical education institutions share the responsibility of developing and maintaining a well-trained and competent workforce.
- Pre-service and early-career education are critical times for building awareness and empowering clinicians to proactively engage in training, embed sustainable behaviours into their day-to-day work and improve their clinical practice.
- Training should address individual and organizational factors influencing diagnostic decisions, including perceptions, preferences, attitudes *(20)*, cognitive bias, resistance to change, and cultural factors such as developing skills for withstanding pressure from patients or relatives to conduct tests or provide antimicrobials.
- Training must be dynamic and accessible, and content should be up to date. A variety of modalities, such as practical workshops and case-based learning, delivered during orientation and/or in-training sessions can help clinicians apply theoretical knowledge to their clinical practice.
- Informal discussions are an opportunity to gain insights into diagnostic testing and clinical management of cases that foster learning and improve patient outcomes.
- Multidisciplinary meetings offer opportunities to discuss individual patient cases, and to identify broader learning opportunities where diverse perspectives can provide insights into systemic issues, diagnostic challenges and potential areas for improvements in practice.

WORKFORCE CULTURE – STRENGTHENING INTERDISCIPLINARY COMMUNICATION AND COLLABORATION

- Clinical decision-making, particularly when navigating complex diagnostic challenges, benefits from collaboration among multidisciplinary teams of health-care professionals, including microbiologists, clinicians, infectious disease and IPC specialists, and clinical pharmacists.
- Advocating and fostering an organizational culture that prioritizes patient safety, clinical accuracy and continuous improvement, valuing interdisciplinary collaboration and communication and good clinical diagnostic stewardship as part of good-quality health care.
- Breaking down silos and creating open channels of communication that encourage the rapid sharing of information; all clinicians should be actively engaged in embedding clinical diagnostic stewardship into their day-to-day practice.
- Leading by example, senior clinicians can champion good practice, driving adherence to protocols, fostering multidisciplinary collaboration, on-the-job training and sharing best practices within clinical teams.
- Empowering clinicians to work effectively and derive job satisfaction, ensuring manageable clinical workloads.

6. Case studies

General objectives

1. To promote good clinical diagnostic stewardship practices, focusing on using the clinical presentation of patients to guide ordering microbiological tests appropriately – taking the *right* test(s) at the *right* time in the *right* way from the *right* patients.
2. To avoid unnecessary testing or ordering tests that are unlikely to change the management of the patient.
3. To understand the importance of correct specimen collection and timing, sample labelling, storage and transportation to the laboratory to reduce the risk of specimen rejection in the laboratory.
4. To understand the importance of correct interpretation of microbiological test results for good antimicrobial stewardship, including empiric and directed/targeted antibiotic treatment and implementing de-escalation interventions.

Disclaimer: The case studies are not intended to indicate WHO-recommended management of specific clinical situations but rather to highlight examples of clinical diagnostic stewardship. Before conducting training, the case studies should be reviewed and adapted to the local context as appropriate.

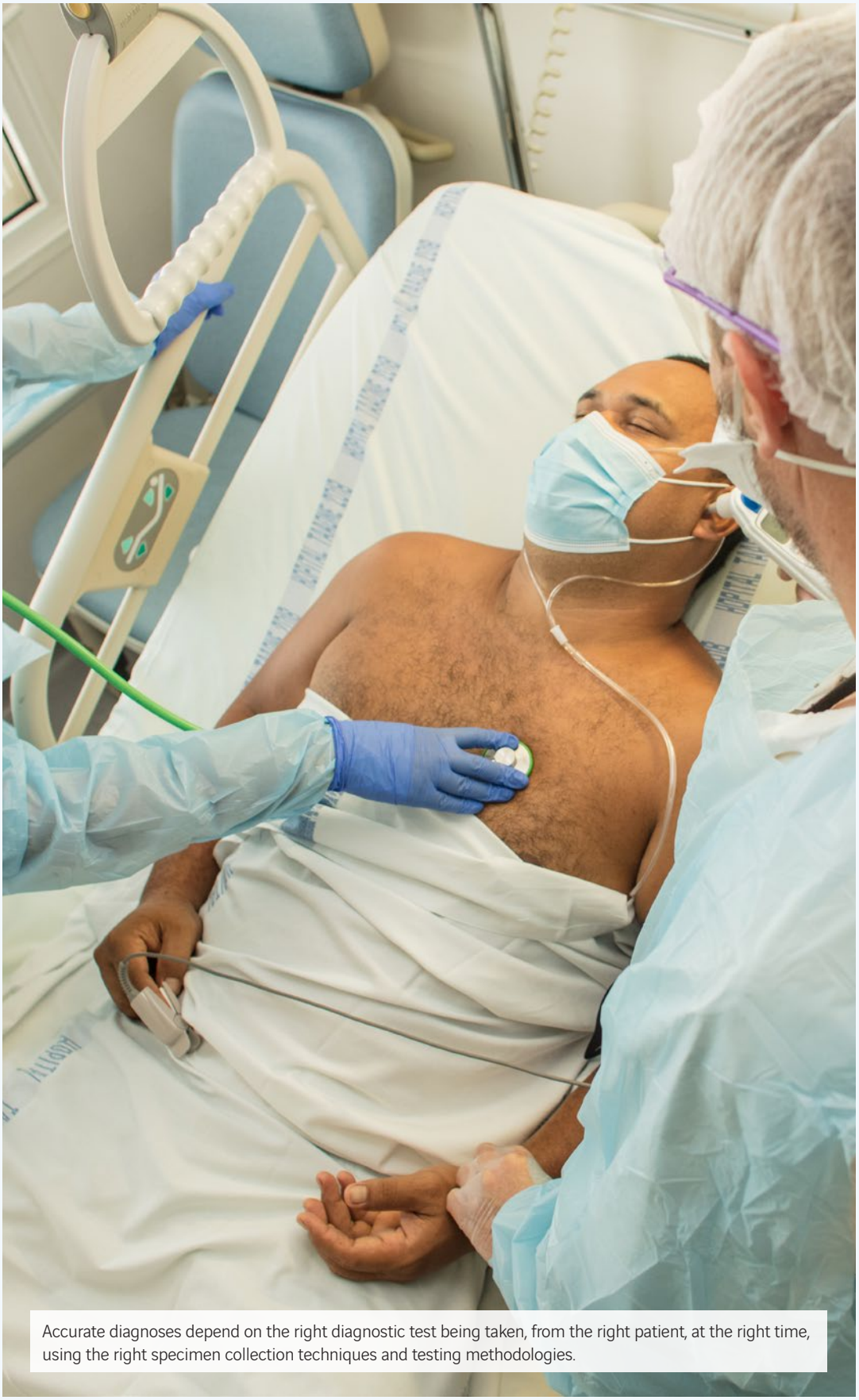
Summary learning points

1. The best-value microbiology testing comes from samples taken:
   - from patients with clinical symptoms and signs suggesting infection;
   - before antibiotics are given to the patient;
   - from sterile sites wherever possible; and
   - using a sterile technique to avoid contamination.

2. To avoid low-value microbiology testing:
   - do not take samples from people without a clinically suspected infection;
   - train staff in correct sampling techniques to minimize contamination of samples; and
   - take samples before giving antibiotics (but do not delay starting antibiotics in patients with sepsis/meningitis).

3. When interpreting microbiology results:
   - discourage samples from patients without clear symptoms and signs of infection;
   - encourage taking appropriate blood cultures from patients with clinical signs of sepsis;
   - interpret results from non-sterile sites with care, such as samples from urine, wounds and the respiratory tract; and
   - think critically about colonization versus infection when assessing reports from non-sterile sites and do not treat colonization.

Adult case studies



Accurate diagnoses depend on the right diagnostic test being taken, from the right patient, at the right time, using the right specimen collection techniques and testing methodologies.

Case 1

Mr J is a 34-year-old man who presented extremely unwell with a one-day history of sore throat and headache followed by vomiting and confusion. He has a fever of 39 °C, hypotension (systolic blood pressure is 85 mmHg) and tachycardia (heart rate 120 beats per minute), requiring resuscitation with IV fluids initially, followed by inotropic support in the intensive care unit (ICU).

Two sets of blood cultures were immediately taken. A lumbar puncture was performed which revealed normal cerebrospinal fluid (CSF). A broad-spectrum antibiotic – IV meropenem – was administered empirically after blood cultures had been taken. At 24 hours these blood cultures identified a *Streptococcus pyogenes* which was penicillin susceptible.

On Day 2, treatment for Mr J was changed from meropenem to IV benzylpenicillin, and then to oral antibiotics from Day 4 to complete treatment.

Learning point – The blood culture allowed de-escalation and targeting of antibiotic treatment, limiting use of meropenem even in a very unwell patient with sepsis in the ICU.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
Would you have requested blood cultures for this patient? Why? Why not? What are the indications for taking blood cultures?	Indications for taking blood cultures: • This patient has sepsis, presenting with hypotension and fever, and needing inotropic support. Patients with sepsis/suspected sepsis should have blood cultures taken. Sepsis is defined by clinical evidence of systemic compromise in a person with suspected infection. This patient had hypotension and confusion, which are features of haemodynamic compromise due to sepsis. Other important features to look for include tachypnoea, tachycardia and cool peripheries, and consider (if available) biochemical markers such as a high serum lactate. • The history suggests meningitis as a possible source for sepsis. Blood cultures are important for diagnosing bacterial meningitis *(21)* as they can be positive even when the CSF is negative, and are usually quicker and easier to perform than lumbar puncture. Both sepsis and bacterial meningitis are medical emergencies, and patients should receive antibiotics as soon as possible. Ideally, tests should be performed before starting antibiotics but taking clinical samples should not delay starting antibiotics.
Collecting microbiological specimens	
How many blood cultures would you advise should be taken?	• Where resources allow, two sets of blood cultures should be taken prior to starting antibiotics, without delay in administration of antibiotics. One set of blood cultures consists of two bottles (one anaerobic and one aerobic). The two sets can be taken by blood draws that are taken close together in time, from two different peripheral sites.

Laboratory processing including species identification and susceptibility testing	

Would you have undertaken AST for this isolate (*Streptococcus pyogenes*)?
Why? Why not?
When is AST indicated?
	Indications for AST include:
	• Clinically significant pathogen – causing infection (not colonization) that requires treatment.
	  • Blood should be sterile. The isolation of *Streptococcus pyogenes* from blood is consistent with this patient's clinical syndrome of acute sepsis. This is a significant infection that requires treatment. *Mortality is likely to be high without rapid antibiotic treatment.*
	• Pathogen with unpredictable susceptibility pattern.
	  • Clinically, *Streptococcus pyogenes* remains universally susceptible to penicillin *(22)*. Therefore, many laboratories do not undertake AST for this organism. *In this case, AST is not needed because susceptibility is predictable.*
	  • Very rarely *other* antibiotics may need to be used (for example, if the patient has severe penicillin allergy) and AST may be required.
	• Clinical failure on initial/first-line therapy.
	  • *Not relevant in this case.*
	• Infection control/public health/surveillance.
	  • *Not usually required for this pathogen.*

Interpreting and acting on microbiological results	
Is it reasonable to switch from meropenem to the narrow-spectrum benzylpenicillin?	Yes. Penicillin usually has the lowest minimum inhibitory concentration for *Streptococcus pyogenes*, that is, a lower dose of penicillin kills *Streptococcus pyogenes* compared to the dose needed for other drugs. Penicillin will kill *Streptococcus pyogenes* just as well (potentially better) than meropenem and cause less damage to commensal flora. *The WHO AWaRe antibiotic book* suggests using cefotaxime or ceftriaxone with either amikacin or gentamicin in cases of sepsis of unknown origin. Meropenem may be considered in cases of sepsis associated with likely intra-abdominal infection. Factors to consider when selecting empiric antibiotic treatment include the most likely site of primary infection, the infecting pathogens, the local pattern of AMR and local guidance.

Case 2 *(23)*

Mrs J is an 82-year-old woman who presented with delirium and fever. On history and examination no obvious source of infection was evident. Her chest X-ray was normal.

Blood cultures and urine cultures were taken prior to starting empiric antibiotic therapy with IV ceftriaxone. Given that she was delirious, an in-out catheter was used to collect a clean sample of urine.

The next day the laboratory reported that the blood cultures were negative, but the urine white cell count was > 1000 x10^6/L (normal < 10 x10^6/L) and culture revealed > 10^8 organisms/L of *Escherichia coli* susceptible to amoxicillin + clavulanic acid, cotrimoxazole, nitrofurantoin and ceftriaxone, and resistant to amoxicillin. The patient rapidly improved after a dose of IV ceftriaxone and was shifted to oral cotrimoxazole after 24 hours and discharged.

Learning point – The appropriate sampling of urine for microscopy, culture and AST allowed a clear diagnosis to be made and early targeting of antibiotic therapy to the pathogen. It also allowed timely switch from IV to oral therapy thus enabling the patient to minimize her time in hospital and avoid hospital-associated complications such as physical functional decline and delirium that can commonly occur in older people.

Questions and discussion points

Clinical assessment and requesting microbiological tests

Would you have requested a urine culture for this patient? Why? Why not?

What are the indications for taking a urine sample?

- Urine culture is indicated for symptomatic patients with suspected upper-urinary-tract infection and cases of suspected lower-urinary-tract infection if the patient is at risk of complicated and/or recurrent UTI:
  - Upper-tract symptoms = flank pain/tenderness, fevers, rigors, vomiting
  - Lower-tract symptoms = dysuria, frequency, urgency.

  This patient does not have clear localizing signs of UTI.
- In older patients, urine culture is indicated if infection is suspected and the patient either has:
  - localizing urinary symptoms *or*
  - non-localizing symptoms (fever, confusion) *and* no symptoms to suggest infection at another site.
- In this instance urine culture is indicated, given the non-localizing symptoms (fever, confusion) *and* no signs of another source of infection (no respiratory symptoms/signs, no suggestion of a skin source or an intra-abdominal source of sepsis).

Collecting microbiological specimens

How can urine samples be collected?

What are the advantages and disadvantages of different urine sampling methods and sample types?

- Urine samples may easily become contaminated with skin flora.
- Taking a clean catch or midstream urine sample requires some degree of patient cooperation.
- Indwelling catheter samples are prone to contamination, especially if the catheter has been in for a long time. The specimen should be obtained aseptically, either from the sampling port of the catheter tubing or by direct aspiration of the tubing using a sterile needle and syringe, not from the drainage bag.
- An in-out catheter sample may be a useful alternative in some situations but still carries a risk of introducing infection.

Interpreting and acting on microbiological results	
Is this urine culture result significant?	• A positive urine culture alone is not always a sign of a UTI as bacterial colonization of urine is common. Other factors, such as the urine white cell count as well as clinical features, are required to make the diagnosis. • There is no urine white cell count cut-off that indicates an infection, but the higher the count, the higher the probability of infection. The presence of a catheter can be associated with a high urine white cell count even when there is no infection. This patient has a high urine white cell count that likely reflects a UTI. • The patient has fever, confusion, a high urine white cell count and a high bacterial load in the urine culture, so a diagnosis of UTI can be made.
Laboratory processing including species identification and susceptibility testing	
Would you have undertaken AST for this isolate (*Escherichia coli*)? Why? Why not? When is AST indicated?	Indications for AST include: i. Clinically significant pathogen – causing infection (not colonization) that requires treatment. • Given the fever and delirium (and positive urine findings), this patient has a UTI, most likely involving the upper-urinary tract (for example, pyelonephritis +/– bacteraemia). *Antibiotic treatment is indicated*. ii. Pathogen with unpredictable susceptibility pattern. • *Escherichia coli* has acquired multiple resistance mechanisms, which vary geographically. Generally antimicrobial susceptibility cannot be reliably predicted. *It is reasonable to undertake AST*. iii. Clinical failure on initial/first-line therapy. • *Not relevant in this case*. iv. Infection control/public health/surveillance. • *Escherichia coli* in urine is a pathogen–specimen type combination targeted for surveillance as part of GLASS *(24)*. *Escherichia coli* easily acquires resistance and can serve as an indicator of drug resistance in a given population.

Case 3

Ms X is a 24-year-old woman who presents with a two-day history of a stinging and burning sensation when she passes urine and the need to urinate frequently. She has some lower-pelvic discomfort but is otherwise afebrile and well.

Ms X was reassured and sent home with advice to drink plenty of fluids, take paracetamol if needed and to come back if her symptoms did not resolve.

Learning point – This is a patient of reproductive age with localizing symptoms and signs of a lower-urinary-tract infection. There are no features to suggest upper-urinary-tract infection, so this is likely cystitis. In this situation, there are several possible pathways of management.

Systematic reviews suggest that for otherwise well pre-menopausal women, lower-urinary-tract symptoms will often resolve spontaneously without needing antibiotics. Watchful waiting may be appropriate, with use of analgesia as needed. If, however, the symptoms are very distressing or do not improve after a few days of monitoring, then empiric antibiotics may be reasonable.

Questions and discussion points

Clinical assessment and requesting microbiological tests	

Should a midstream urine sample have been sent from this patient?	• A midstream urine sample does not always need to be sent in low-risk women of reproductive age with lower-urinary-tract symptoms alone. It is reasonable for empiric antibiotics that treat cystitis to be selected (for example, nitrofurantoin or trimethoprim), based on local guidance.
	• A midstream urine sample is, however, recommended if a pre-menopausal woman with cystitis:
	  • has recurrent UTI and repeated antibiotic exposure
	  • has anatomical abnormalities in the urinary tract
	  • is immunosuppressed
	  • is pregnant
	  • has an uncertain diagnosis
	  • fails empiric antibiotic therapy.

Case 4 *(25, 26)*

Mr X is a 48-year-old man with diabetes who has had long-standing problems with ulcers on his feet. He has taken multiple courses of antibiotics in the past to help heal his ulcers – most recently two weeks of cephalexin.

He is systemically well and there is no evidence of cellulitis surrounding the ulcers. A swab of the ulcer base was taken that has now grown multidrug-resistant *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). You are asked about antibiotic therapy: should he start meropenem and vancomycin?

Learning point – Chronic ulcers become colonized with bacteria. In people who are systemically well, ulcers with no signs of cellulitis do not require wound swabs or antibiotic treatment. Swabs in this setting often demonstrate colonizing bacteria and drive unnecessary antibiotic use.

In this case the team decided that the bacterial growth represented colonization and not infection. They advised no further antibiotics. Instead, they focused on wound dressings, improved glycaemic control, managing other risk factors for vascular disease, strategies to protect his feet from injury and investigations to assess for peripheral vascular disease.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
Would you have requested a wound swab for this patient? Why? Why not? What are the indications for taking a wound swab for culture?	• A wound swab is not indicated in this situation. • Without clinical signs of infection, bacterial growth from the swab is not relevant for clinical management of the patient. Chronic ulcers are almost universally colonized with microorganisms. Often patients with chronic ulcers have received multiple courses of antibiotics, so their "normal" colonizing flora becomes resistant. MRSA and *Pseudomonas* can be frequent colonizers of ulcers in this situation. • Ulcer swabs or antibiotics are not necessary for the management of a leg ulcer without evidence of clinical infection.

Case 5

Mr G is a 55-year-old previously well man who was admitted with a fever of 38 °C, cough and pleuritic chest pain. His chest X-ray on admission showed evidence of consolidation consistent with a diagnosis of pneumonia.

Blood cultures were taken in the emergency department prior to starting empiric antibiotic therapy with oral amoxicillin + clavulanic acid.

The blood cultures have identified a methicillin-resistant *Staphylococcus epidermidis* (a CoNS) and questions are raised about the need to add vancomycin.

Learning point – CoNS in blood cultures are frequently contaminants. In this case of a patient with pneumonia, it is very unlikely to be a pathogen. Contaminated cultures consume a lot of resources in the laboratory and sometimes lead to unnecessary antibiotic treatment for patients. It is important to ensure appropriate/correct sterile technique to avoid contamination at the time of taking samples.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
Would you have requested a blood culture for this patient? Why? Why not?	• *The WHO AWaRe antibiotic book* suggests collecting blood cultures from patients with severe pneumonia to guide antimicrobial treatment.
Interpreting and acting on microbiological results	
Do you think the *Staphylococcus epidermidis* result is significant in this case?	Blood culture contamination: • *Staphylococcus epidermidis* does not cause community-acquired pneumonia. It may, uncommonly, cause infections at other sites; however, the clinical and radiological features make the probability of community-acquired pneumonia with a contaminated blood culture more likely than a *Staphylococcus epidermidis* infection at another site. • CoNS may be pathogens in rare circumstances, typically where prosthetic material is present (for example, intravascular line infections, prosthetic valve endocarditis, intravascular graft infections and prosthetic joint infections). In these cases, evidence for true pathogenicity comes when the same bacteria are repeatedly isolated from blood cultures and associated with a relevant clinical syndrome. If in doubt, seek expert advice from a microbiology or infectious disease specialist. • Blood culture contamination occurs when there is growth of an organism in a blood culture bottle that is not circulating in the patient's blood at time of collection, most often coming from the patient's skin where it is part of the normal bacterial flora. • Contamination rates can be reduced by focusing on careful aseptic technique during blood draw. Consider refresher training for staff.

Should vancomycin be added to treat the *Staphylococcus epidermidis*?	• No, contamination is most likely. *Therefore, vancomycin should not be added*. • *Staphylococcus epidermidis* is a common skin commensal organism. In this case, with the strong clinical and radiological diagnosis of community-acquired pneumonia, it is reasonable to do nothing further with respect to this contamination event.
What should be done next for this patient's management?	• Monitor closely for clinical improvement on the antibiotic combination directed to community-acquired pneumonia. • Complete treatment with oral antibiotics for five days unless there are complications or the patient is not clinically stable at five days. • Use the opportunity to discuss smoking cessation and other preventive management, such as annual influenza vaccination.

Case 6

Ms L experienced a sudden loss of consciousness and was found to have had an intracerebral haemorrhage. She is slowly improving but has been in the ICU for five days and is still intubated. She is afebrile and her chest X-ray is clear.

The nurse aspirated thickened secretions from the endotracheal tube, which were sent to the laboratory for culture as a routine practice.

The tracheal aspirate is growing a small amount of mixed upper-respiratory flora with some *Staphylococcus aureus* also identified. You have been asked if antibiotics are required.

Learning point – If the chest X-ray is clear and the patient has no other signs of pneumonia, then this is likely contamination and does not require antibiotic treatment. Endotracheal tubes commonly become colonized with bacteria from the upper-respiratory tract.

Sputum samples should only be sent if there is a clinical reason to suspect an infection. Sending routine samples from devices is not necessary and can lead to unnecessary antibiotic therapy.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
Would you have requested a tracheal aspirate in this situation? Why? Why not?	• This patient has no signs of ventilator-associated pneumonia (VAP). • VAP is defined as acute illness affecting the lungs caused by pathogens in the hospital setting and presenting 48 hours or more after admission while the patient is on a ventilator. • A tracheal aspirate should not have been sent from this patient.
Interpreting and acting on microbiological results	
Is the culture result significant?	• *Staphylococcus aureus* is a normal commensal organism in the upper-respiratory tract. It is, therefore, not unexpected to find it growing from this site. • Based on the culture result, the growth of *Staphylococcus aureus* is neither significant (that is, it is present in low quantities) nor predominant (that is, it is not present in higher quantities than commensal flora). Therefore, there is no microbiological evidence to suggest infection. This culture is consistent with normal colonization.
Should this patient receive treatment for this culture result?	• No. There is no clinical or microbiological evidence of *Staphylococcus aureus* VAP.

Case 7

Ms S has been in the ICU after a motor vehicle accident in which she experienced multiple fractures and a closed head injury. She has been improving and will soon be moved to the surgical ward.

The ICU team removed her central venous catheter and sent the tip to the laboratory for culture as a routine activity. The tip has grown *Acinetobacter baumannii*, and a question is raised about whether antibiotic treatment should be given.

Learning point – Routine culture of catheter tips upon removal is not recommended, except when clinical signs and symptoms suggest bloodstream infection or there is evidence of exit site infection – that is, erythema, and/or pus from the site. If the patient is well, these cultures only consume resources unnecessarily and can lead to unnecessary antibiotic therapy.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
What are the indications for taking a catheter tip sample? Would you have sent the catheter tip for culture from this patient? Why? Why not?	• Indications include suspected bacterial infection – symptoms consistent with a central-line infection (for example, fever, rigors, hypotension) *and* no other obvious site of infection. • If a line infection is suspected and a central venous catheter tip is sent for culture, concurrent peripheral blood cultures should also be sent and the results compared. If both cultures grow the same organism with the same susceptibility pattern, this suggests bloodstream infection rather than colonization. • In this case, there are no features suggesting sepsis due to central-line-associated bacteraemia and no exit site infection, so this tip should not be sent for culture.
Interpreting and acting on microbiological results	
Is the growth of *Acinetobacter baumannii* significant? Should the *Acinetobacter* be treated with antibiotics?	• *Acinetobacter* frequently colonizes foreign bodies. The growth of this organism without clinical symptoms and without growth from a concurrently collected blood culture is consistent with colonization, *not* infection. • No. The growth is not significant, that is, there is no infection, and should not be treated with antibiotics.
Laboratory processing including species identification and susceptibility testing	
Should AST be performed on this isolate (*Acinetobacter baumannii*)?	• In this case, where the *Acinetobacter baumannii* isolate represents colonization, not infection, nothing more needs to be done. • However, if multidrug-resistant *Acinetobacter* (for example, carbapenem resistant) has caused hospital outbreaks in the setting, it might be appropriate to request AST, so that enhanced infection control interventions, such as isolation of the patient, can be implemented if the organism is found to be multidrug resistant.

Case 8

Mr P is 75 years old and has had an indwelling urinary catheter for several weeks while awaiting prostate surgery.

A nurse noted that the urine looked cloudy. Urine samples were taken that revealed an elevated white cell count and growth of *Escherichia coli*. Antibiotic AST suggests it is carrying an extended-spectrum beta lactamase (ESBL).

The question is raised about the most appropriate antibiotic therapy.

Learning point – All urinary catheters will eventually become colonized with bacteria, and elevated white cell counts in urine are not unusual in catheterized patients. If Mr P is systemically well, there is no need to send a urine sample for culture and no need to treat with antibiotics.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
Would you have requested a urine culture for this patient? Why? Why not?	• Cloudy urine is not an indication for urine culture. • This patient is not symptomatic. • There are limited indications for testing asymptomatic individuals, related to the risk of subsequent symptomatic infection. This may include people undergoing procedures which will penetrate the wall of the urinary tract. • However, in Mr P's case, prostate surgery will penetrate the wall of the urinary tract and pre-procedural testing is an indication for urine culture.
Interpreting and acting on microbiological results	
Is this urine culture result significant? Should the growth be treated with antibiotics?	• A positive urine culture in an asymptomatic patient indicates bacterial colonization and does not require treatment, except in pregnant women or in patients undergoing urological procedures in which bleeding is anticipated. • A catheter can cause inflammation and irritation to the bladder and urethra, leading to a high urine white cell count without infection being present. • The presence of a foreign body increases the likelihood of asymptomatic bacteriuria, that is, bacterial colonization. • In this patient, asymptomatic bacteriuria is associated with an increased risk of post-procedural sepsis during prostate surgery. Targeted antimicrobial therapy based on susceptibility testing of *Escherichia coli* should be given before the procedure.

Case 9

Ms T is 84 years old and has dementia. Her family says that three days ago she seemed more confused than usual. That day she had moved to a new room in her aged care home and staff needed to spend a great deal of time reorientating her.

She was afebrile and denied any urinary symptoms, but a urine sample was sent which grew *Proteus mirabilis*.

Today she seems much more settled. Should antibiotics be started?

Learning point – There is a reasonable alternate explanation for her confusion, and she does not have any other clinical symptoms suggesting infection. It is most likely that the urine finding represents asymptomatic bacteriuria and that her confusion was related to moving to a new room. Ms T does not require antibiotic treatment at this time, but her clinical condition should continue to be closely monitored.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
Would you have requested a urine culture for this patient? Why? Why not?	• Look for and address non-infective causes of confusion in elderly people before sending microbiological tests or starting antibiotic treatment, if they are otherwise clinically stable. • Asymptomatic bacteriuria is very common in elderly women and does not need antibiotic treatment. • If the patient is asymptomatic, then even if bacteriuria is associated with pyuria (white cells in urine), no treatment is needed. • In this case, Ms T's clinical condition should be monitored closely. If she deteriorates, then empiric antibiotic treatment for cystitis may be considered.

Case 10

Mr W has a long history of smoking cigarettes and a chronic cough. He has no new symptoms and is otherwise well.

He coughs up a sample that looks like saliva with a small amount of sputum which is sent for culture and AST. He is started on empiric amoxicillin.

The microbiology report of the sputum describes scant polymorphs and grows mixed upper-respiratory flora.

Learning point – Avoid sputum culture in mild cases as patients may be colonized by multiple bacteria, making results difficult to interpret, especially if the quality of the sputum sample is poor.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
Would you have requested a sputum culture for this patient? Why? Why not? What other testing may be considered?	• It is unhelpful to send poor-quality samples for culture. Sputum will be colonized with respiratory tract flora. AST and targeted antibiotic treatment are not indicated. • WHO suggests implementing an objective measure of sputum quality (including for example, whether it is salivary or mucopurulent, and/or the ratio of white blood cells to epithelial cells) to guide decisions on whether to set up the sample for culture. • Consider specific investigations for TB in endemic settings, especially in high-risk patients (for example, patients living with HIV). A rapid molecular test performed on a single sputum specimen is the preferred first-line diagnostic test for pulmonary TB and to detect rifampicin resistance. • If a good-quality sample cannot be obtained and clinical infection is strongly suspected, an alternative sampling technique may be considered, for example, induced sputum or bronchial lavage or washings.

Case 11

Mr B is a 60-year-old male who presents to hospital with chest pain, shortness of breath and sweats. Based on his symptoms and electrocardiogram (ECG) findings, a diagnosis of ST-segment elevation myocardial infarction is made. He undergoes thrombolysis, and his chest pain, breathlessness and ECG changes improve.

Later that day, his respiratory viral PCR from a nose and throat swab returns a "Detected" result for SARS-CoV-2, the virus that causes COVID-19. His chest X-ray is clear.

On further questioning, Mr B has no respiratory symptoms, but he remembers having a few days of runny nose and headache two weeks ago. His son and daughter were also unwell at the same time with similar symptoms.

Learning point – PCR testing is very sensitive and can detect very small amounts of microbial DNA or RNA, but the PCR test cannot differentiate between active and recent past (and potentially resolved) infection.

Understanding how "Detected" or "Not Detected" results relate to the patient's current presentation is very important when interpreting their significance and has implications for treatment and for local infection control policies.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
What does this PCR test result mean? Does Mr B have COVID-19?	• The patient does not currently have symptoms suggesting active COVID-19, but he may have had COVID-19 a couple of weeks ago. • Most likely, this PCR result indicates COVID-19 infection in the recent past. • COVID-19 can increase the risk of myocardial infarction.
Should Mr B be treated for COVID-19?	• Antiviral medication for COVID-19 is most effective when started soon after symptoms begin. • As it is likely that Mr B's COVID-19 related symptoms occurred two weeks ago, antiviral treatment is not indicated now.
Should Mr B be isolated from other patients?	• This depends on local infection control policies, but it is probably reasonable not to isolate patients whose symptom onset was more than 14 days ago. • Some patients with recent infection who are no longer infectious still have a "Detected" PCR result. • Mr B probably does not need to be isolated as his history suggests his respiratory symptoms occurred two weeks ago; however, the timing should be confirmed and local infection prevention and control policies followed.

Paediatric case studies

Paediatric cases require the same approach as adult cases: ordering the right diagnostic test, for the right patient at the right time, and interpreting and acting on the results appropriately.

Paediatric case 1

R is a 4-month-old boy who presented with irritability and a two-day history of fever, poor feeding and decreased urine output; his last wet diaper was 12 hours prior to presentation. His immunizations were up to date. He was uncircumcised. He was febrile and tachycardic, and moderate dehydration was suspected, prompting IV fluid administration.

Initial urinary catheterization yielded no specimen as the bladder was empty. Urine was subsequently collected using a perineal urine bag attached to the genital area, with dipstick testing showing 3+ white cells and positive nitrites. Repeat catheterization using sterile technique was performed to obtain a specimen suitable for urine culture. Empirical IV ampicillin and gentamicin were started for suspected UTI.

Urine culture grew 10^5 colony-forming units (CFU)/mL *Escherichia coli*, susceptible to cephalexin and gentamicin but resistant to ampicillin. Abdominal ultrasound for urogenital anomaly screening was normal. On day 4, the patient had improved clinically, was stepped down to oral cephalexin, and he was discharged to complete a seven-day course of therapy at home.

Learning point – Do not send urine cultures from a perineal urine bag in children, as these samples are often contaminated with bacteria colonizing the urogenital area.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
When and why do you suspect UTI in febrile infants?	• Febrile infants without an identifiable source of infection should be evaluated for UTI, particularly if they appear ill or are younger than 3 months of age. Young children are unable to report dysuria caused by UTI. Infants younger than 3 months are at higher risk for serious bacterial infections, including UTI. • Uncircumcised boys are also at increased risk; however, circumcision practices vary widely depending on local cultural and religious factors.
Collecting microbiological specimens	
How do you collect and manage urine specimens in small children? What other microbiological tests might you consider?	• A perineal urine bag may be used for urinalysis or dipstick testing as an initial screening method in children who have not yet established spontaneous voiding (those wearing diapers). • Collection of urine for culture using a perineal urine bag should be avoided, as samples frequently become contaminated with perineal flora and may yield false positive test results. Urine should instead be obtained by catheterization or another sterile method, such as a clean-catch specimen. This is used as a non-invasive alternative to collecting urine by catheterization in children with established voluntary voiding. The periurethral area should be cleaned with sterile saline-soaked gauze, after which the child voids spontaneously, and midstream urine is collected in a sterile container. • Urine specimens should be sent immediately (within two hours of collection) to the laboratory at room temperature. When immediate delivery to the laboratory is not possible, refrigerate the urine at 2–8 °C (for no more than 24 hours) to prevent bacterial overgrowth. • In patients requiring hospitalization, blood culture should be considered where possible before starting antibiotic treatment to guide treatment.

Laboratory processing, including species identification and susceptibility testing	
How is urine culture processed and when is susceptibility testing performed?	• Urine culture is considered positive when bacteria are above a certain minimum cut-off concentration in symptomatic patients (for example, ≥ 10^5 microorganisms/mL of urine). That can vary between laboratories. Refer to local guidelines for guidance.
Interpreting and acting on microbiological results	
How should susceptibility results be interpreted and how should this case be treated?	• The *WHO AWaRe antibiotic book* suggests using cefotaxime or ceftriaxone and/or amikacin or gentamicin for severe cases – especially in locations where ESBL-producing isolates are highly prevalent. • The most appropriate empiric antibiotics for cases of UTI can be determined by referring to local data on AMR resistance, including on ESBL- or carbapenemase-producing Enterobacterales. • In this case, the *Escherichia coli* UTI was treated empirically with ampicillin and gentamicin. Although the isolate was resistant to ampicillin, it remained susceptible to gentamicin, which was sufficient to achieve a clinical response. Step-down therapy to an appropriate oral antibiotic is recommended once the patient can tolerate oral intake.

Paediatric case 2

M is an 8-month-old girl who presented with a five-day history of fever, cough and respiratory distress. She had received immunizations only at birth. There was no family history of TB. On presentation, she was febrile, tachypnoeic and cyanotic; supplemental oxygen and IV fluids were initiated. Chest X-ray showed right-middle-lobe infiltrates, and laboratory testing revealed a significantly elevated white blood cell count of 26 000/μL with 80% neutrophils.

Nasopharyngeal swab culture and blood culture were obtained, and empirical IV ampicillin was started for suspected bacterial pneumonia. By the following day, M's clinical condition had improved.

Blood cultures grew *Streptococcus pneumoniae* susceptible to penicillin, while the nasopharyngeal swab grew MRSA. *Streptococcus pneumoniae* was considered to be the causative pathogen, and MRSA was interpreted as nasal colonization.

On day 4, treatment was stepped down to oral amoxicillin to complete a seven-day course of therapy. She was referred to her primary care clinic for catch-up immunization.

Learning point – Upper-respiratory-tract cultures should not be relied upon to guide therapy for suspected bacterial pneumonia because bacteria colonizing the upper airway may differ from the causative pathogen in the lower-respiratory tract or lungs.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
When and why do you suspect bacterial pneumonia and what tests should be performed?	• Febrile children presenting with respiratory symptoms, tachypnoea and respiratory distress should be suspected of having lower-respiratory-tract infections, such as bronchitis, bronchiolitis or pneumonia. If a chest X-ray is available, it may help differentiate bronchiolitis from pneumonia. Bronchiolitis typically presents with hyperinflation and air trapping without focal infiltrates, whereas pneumonia is more commonly associated with focal or lobar infiltrates. Bronchitis typically has unremarkable chest X-ray findings. • Blood cultures may be helpful if severe bacterial pneumonia is suspected, as bacteraemia can occasionally be present, particularly in children who are unimmunized or incompletely immunized against *Streptococcus pneumoniae* or *Haemophilus influenzae* type b. Bacteraemia should be suspected in children with high fever or hypothermia, a toxic or ill appearance with abnormal vital signs, or elevated inflammatory markers (white blood cell count or C-reactive protein).
Collecting microbiological specimens	
Should you obtain respiratory specimens in children?	• Sputum samples cannot usually be obtained from children because they are unable to expectorate sputum. Upper-respiratory-tract cultures often reflect colonization rather than the causative pathogen of lower-respiratory-tract infection; therefore, they should be avoided in children with respiratory tract infections.

Interpreting and acting on microbiological results	
How should susceptibility results be interpreted and how should this case be treated?	• Nasopharyngeal swab cultures frequently detect colonizing organisms (in this case, MRSA). In this patient, detection of *Streptococcus pneumoniae* in the blood culture confirmed the causative organism. If the child responds well to initial antimicrobial therapy and the isolate is susceptible to penicillin, and if bacterial meningitis is clinically unlikely, therapy can be switched to an appropriate oral antibiotic. • *The WHO AWaRe antibiotic book* suggests treatment with antibiotics for three days if the child has no chest indrawing and the area has low HIV prevalence; or five days if the child has chest indrawing and/or in areas of high HIV prevalence. If the child has severe disease and is not clinically stable at day 5, consider continuing treatment and look for complications such as empyema. • Even after invasive pneumococcal disease, protection against future infections is not guaranteed because multiple pneumococcal serotypes exist. Therefore, catch-up pneumococcal vaccination, if available, should be arranged for children who are not fully immunized to prevent infection with other serotypes. It should be noted that in some countries pneumococcal vaccination is not included in routine immunization programmes.

Paediatric case 3

L is an 8-year-old girl with cerebral palsy who is bed-bound with a tracheostomy and gastrostomy. She presented with a three-day history of fever, increased respiratory secretions and respiratory distress, with two prior episodes of pneumonia in the past year. Chest X-ray showed new bilateral lower-lung infiltrates.

Sputum Gram stain from a tracheostomy sample revealed mixed organisms, predominantly Gram-negative cocci. Empiric amoxicillin + clavulanic acid given through the gastrostomy tube was initiated for suspected bacterial pneumonia. She improved clinically and became afebrile.

Sputum culture later grew *Moraxella catarrhalis, Pseudomonas aeruginosa* and MRSA. Given her clinical response, she completed a five-day course of amoxicillin + clavulanic acid and was discharged home.

Learning point – In medically complex children, sputum cultures may simultaneously detect both true pathogens and colonizing organisms, and antibiotic therapy directed at all isolated organisms may constitute overtreatment.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
How should organism identification results and clinical response be interpreted?	• Initial Gram staining provides an important clue to the likely causative pathogen. *Moraxella catarrhalis* appears as Gram-negative cocci typically observed in pairs (diplococci), *Pseudomonas aeruginosa* appears as Gram-negative bacilli and MRSA appears as Gram-positive cocci in clusters. Children with a tracheostomy are frequently colonized with multiple organisms. Gram staining generally detects the predominant bacteria, whereas culture may detect both pathogens and colonizing organisms. In this case, Gram-negative cocci were predominant in the sputum specimen, suggesting *Moraxella catarrhalis* as the pathogen. This organism is typically susceptible to amoxicillin + clavulanic acid. • The clinical response to antimicrobial therapy also provides an important diagnostic clue. Patients with bacterial infections generally improve when the causative pathogen is appropriately treated and deteriorate when antimicrobial therapy does not adequately cover the responsible organism. In this case, the patient improved with therapy directed primarily against *Moraxella catarrhalis*. Amoxicillin + clavulanic acid is not effective against *Pseudomonas aeruginosa* and MRSA. Therefore, if *Pseudomonas aeruginosa* or MRSA had been the true pathogens, clinical worsening would have been expected. These organisms were thus more likely to represent colonization rather than true infection. • *The WHO AWaRe antibiotic book* suggests treatment with antibiotics of children with hospital-acquired pneumonia for seven days. If the patient is not clinically stable at day 7, reassess the diagnosis and consider treating for longer.

Paediatric case 4

K is a 2-week-old boy born at 28 weeks of gestation with a birth weight of 1350 grams. He was admitted to the neonatal ICU and required mechanical ventilation for the first week of life. A peripherally inserted central catheter (PICC) was placed on admission for IV fluids. He developed recurrent apnoea requiring re-intubation seven days after initial extubation.

A sepsis workup was performed, and empirical ampicillin and gentamicin were started. The following day, blood cultures grew Gram-positive cocci, prompting the addition of vancomycin. The PICC was removed for suspected catheter-related bloodstream infection (CRBSI), and the catheter tip was sent for culture.

Both blood and catheter tip cultures grew methicillin-resistant coagulase-negative *staphylococci* (CoNS). Follow-up blood culture was negative. Vancomycin was continued for three days after the PICC removal, after which the patient's condition improved and he was successfully extubated.

Learning point – Symptomatic premature infants can develop CoNS sepsis, often related to intravascular devices, although CoNS is often considered a contaminant in other settings.

Questions and discussion points

Clinical assessment and requesting microbiological tests

How should susceptibility results be interpreted and how should this case be treated?	• In symptomatic premature infants, CoNS can be true pathogens causing CRBSI. Prompt removal of the PICC, when feasible, is essential, in addition to appropriate antimicrobial therapy. • Although two sets of blood cultures are generally recommended to differentiate contamination from true bacteraemia, this is often impractical in premature infants because of limited blood volume. • In suspected CRBSI, culturing the catheter tip can be helpful alongside at least one blood culture obtained in an aerobic bottle; anaerobic bottles are often omitted to minimize blood loss, as anaerobic infections are rare in this population.

Paediatric case 5

S is a 7-month-old girl with congenital heart disease (ventricular septal defect) treated with furosemide (a diuretic). Surgical repair is planned when she is older. She presented with a five-day history of fever, cough, wheezing and poor feeding. Her respiratory distress worsened over the preceding day. She had been in contact with her sick older brother, who had a runny nose and cough.

Laboratory testing showed a white blood cell count of 6200/µL with lymphocytosis, while other parameters were within normal limits. A chest X-ray showed no cardiomegaly but showed hyperinflation and air trapping. A respiratory syncytial virus antigen test was positive.

Viral bronchiolitis was suspected. Supportive management was initiated including supplemental oxygen for hypoxia and IV fluids for poor oral intake. Her condition gradually improved. She recovered after seven days and was discharged home.

Learning point – Positive respiratory virus testing can support clinicians to avoid unnecessary antibiotic administration when bacterial co-infection is unlikely.

Questions and discussion points

Clinical assessment and requesting microbiological tests	
What tests should be performed to diagnose respiratory viral disease?	• Viruses are the most common cause of respiratory infections in children. Diagnostic testing includes direct detection methods, such as rapid antigen tests, immunofluorescent assays, PCR and viral culture, as well as indirect detection by serology. The choice of test depends on available tests, resources and clinical needs. • Rapid antigen tests, typically based on immunochromatographic assays, offer several advantages, including low cost, room-temperature storage and rapid turnaround time (5–15 minutes). However, their sensitivity is limited, particularly in cases with a low viral load. PCR is increasingly utilized when available, given its high sensitivity and specificity.
How should respiratory viral disease be treated when viral test results are available?	• Respiratory viral infections are primarily treated with supportive care. • Detection of respiratory viruses can support AMS by reducing unnecessary antibiotic use when bacterial co-infection is unlikely, as indicated in this case by the absence of pulmonary infiltrates and non-elevated inflammatory markers (white blood cell count, C-reactive protein or procalcitonin).

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