Infection and Drug Resistance

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REVIEW

Management of Bacterial and Fungal Infections in the ICU: Diagnosis, Treatment, and Prevention Recommendations

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Abstract: Bacterial and fungal infections are common issues for patients in the intensive care unit (ICU). Large, multinational point prevalence surveys have identified that up to 50% of ICU patients have a diagnosis of bacterial or fungal infection at any one time. Infection in the ICU is associated with its own challenges. Causative organisms often harbour intrinsic and acquired mechanisms of drug-resistance, making empiric and targeted antimicrobial selection challenging. Infection in the ICU is associated with worse clinical outcomes for patients. We review the epidemiology of bacterial and fungal infection in the ICU. We discuss risk factors for acquisition, approaches to diagnosis and management, and common strategies for the prevention of infection.

Keywords: bacterial infection, fungal infection, critical care, diagnostics, therapeutics

Introduction

Bacterial and fungal infections are common diagnoses for patients in the intensive care unit (ICU).[1] In 2017, Vincent et al reported a 24-hour point prevalence survey of 1150 centres in 88 countries.[2] Of 15,165 patients with infection data available, 8135 (54%) had proven or suspected infection and 10,640 (70%) received at least one antimicrobial agent. Secondary infection acquired in the ICU was observed in 1760/8135 (22%).[2] Gram-negative organisms predominated (3540/5259; 67%) in those with clinically significant microbiology and fungal infection accounted for 16% (864/5259) of cases.[2] These data were similar to the previous multinational point prevalence studies, such as EPIC II that was performed in 2009 and reported that 51% of patients were considered infected, antibiotics were prescribed for 71% of patients, and Gram-negative infections accounted for 62% and fungal infections 19% of cases.[3]

Mortality rates in the ICU are higher in patients with bacterial or fungal infection compared to those without infection.[2–9] In-hospital mortality for ICU patients with infection is approximately 30%.[2] Secondary bacterial or fungal infection and the presence of drug-resistant infections are independent risk factors for mortality with an increased odds of death compared to community-acquired infection (OR: 1.32; 95% CI 1.10–1.60).[2]

Infections in the ICU are frequently caused by drug-resistant bacteria and increasingly drug-tolerant/resistant fungi.[3,7,10] Termed antimicrobial resistance (AMR), these infections already have a significant impact on hospitalised patients.

Globally, rates of AMR will vary between regions.[11,12] Gram-negative organisms pose a major challenge including extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriales, derepressed AmpC organisms, carbapenemase-

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producing Enterobacteriales (CPE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa*.[12] Gram-positive challenges include methicillin-resistant *Staphylococcus aureus* (MRSA) and glycopeptide-resistant *Enterococcus* (GRE) *species*.[12]

Antifungal tolerant and resistant fungal infections are an emerging threat,[13,14] not least given the high rate of associated mortality in critical care, and the relative inability to rapidly diagnose and deliver effective antimicrobial therapy.[13] Among fungal pathogens, the global emergence and spread of multidrug-resistant *Candida auris* has caused several healthcare-associated outbreaks.[15–17] Blood stream infections among non-*albicans Candida* species with decreased susceptibility to first-line antifungal therapies including azoles and echinocandins have been reported.[18] Examples include fluconazole and echinocandin resistance in *Nakaseomyces glabrata* (formerly *Candida glabrata*) isolates[19] and the recent emergence of fluconazole-resistant *Candida parapsilosis*. *Candida parapsilosis* has been demonstrated to persist and cause outbreaks in neonatal and adult ICUs.[20–22]

Among filamentous fungi, resistance of *Aspergillus fumigatus*, the most common respiratory fungal pathogen, to triazole antifungal agents is clinically significant. Aspergillus infections caused by azole-resistant strains are seen in both azole-naïve and those who have undergone long-term azole therapy and present a clear challenge in diagnosis and treatment with increased associated mortality.[23] The number of infections caused by moulds with intrinsic resistance to one or more class of antifungal agent is increasing with notable examples including Mucorales, *Fusarium* species, *Scedosporium* species and *Lomentospora prolificans*.[24]

Admission to the ICU is associated with numerous risk factors for the development of nosocomial infection, including ventilator/hospital-acquired pneumonia (VAP/HAP), catheter-associated blood stream infection, surgical site infection, and urinary tract infection (UTI).[3] The use of central venous catheters, invasive mechanical ventilation, sedation and paralysis, complex surgical procedures, broad-spectrum antimicrobial use, and patient immune status all increase patient risk of secondary infections.[2,8] Patient outcomes are often worse for those who experience secondary bacterial and fungal infection in the ICU[3] and place a significant financial burden on healthcare services.[1]

Recent experience during the COVID-19 pandemic highlighted the challenge of bacterial and fungal infections in patients admitted to ICU.[25] Overall, bacterial and fungal co-infection was rare in COVID-19, but in patients admitted to ICU rates were high.[26] It is likely that a breakdown in infection prevention and control (IPC) practices, increased use of broad-spectrum antimicrobials, and changes in the hospital environment brought about by COVID-19 have driven observed outbreaks of multidrug-resistant bacterial infections within the ICU environment during this period.[25,27,28]

Both seasonal influenza[29] and the COVID-19 pandemic[30] have resulted in larger proportions of the critically ill patients at risk of secondary fungal co-infections. Fungal pathogens that have been observed to cause co-infections in patients with COVID-19 include *Aspergillus*, Mucorales and *Candida* species. The epidemiology, clinical and host risk factors, immunological mechanisms, and metabolic responses that underline the pathogenesis of COVID-19 fungal co-infections are complex and reviewed extensively by Hoenigl et al.[31]

This review will explore the diagnosis, management, and strategies for prevention of bacterial and fungal infection in the ICU. It will review current and future diagnostic and management approaches for patients with suspected bacterial and fungal infections in the ICU. It will consider the evidence-base around prevention of secondary infections.

Challenges in the Diagnosis of Bacterial and Fungal Infection in ICU

The diagnosis of infection in ICU patients can be challenging.[32] Organ support may mask traditional diagnostic factors such as features of the systemic inflammatory response syndrome (SIRS) including hypotension or fever and clinical features of specific organ infections.[33] Furthermore, SIRS can often be of non-infective origin. Clinical history and examination may be limited, and diagnostics often have a long turnaround time compared to the urgency with which to make a decision regarding therapeutic strategy.[32] Whilst prediction tools have been developed to support the early detection of sepsis, they remain limited in their overall performance in many cases.[33–35]

Current guidelines recommend that diagnosis of sepsis is based on clinical judgement moving away from the reliance on more objective decision support tools.[32] Early recognition, investigation, and appropriate management are vital to optimise clinical outcomes when sepsis is suspected.[32]

Whilst early appropriate antimicrobial therapy is often associated with superior clinical outcomes for patients with severe infection, unnecessarily broad therapy has been associated with increased mortality and complications for individual patients.[9] Beyond patients with septic shock, there remains controversy around time-to-antibiotic-based guidelines if appropriate diagnostic steps have not been implemented before commencement of antimicrobial therapy.[36]

Appropriate investigation and timely initiation of therapy is vital to deliver optimal care. The formulation of syndromic diagnosis and the use of appropriate diagnostics require an understanding of clinical risk factors and diagnostic tools that are available to support different aspects of clinical decision-making.

Risk Factors for Bacterial and Fungal Infection

Table 1 outlines common risk factors associated with bacterial and fungal infection for frequent infective syndromes within the ICU. Risk of infection will vary between organism, site of infection, patient, and local factors.[2] Compared to the general hospital population, rates of bacterial and fungal infection are often significantly greater within the ICU.[2] Common factors associated with increased risk of infection include intrinsic factors, such as immunosuppression, comorbidities, and critical illness.[10] Modifiable risk factors include organ support, such as mechanical ventilation, haemofiltration and total parenteral nutrition (TPN); surgical procedures; and the requirement for prolonged admission to the ICU.[10]

Epidemiology of drug-resistant infections will likely vary between geographical regions, but common risk factors should be considered for those at risk of carriage and infection with multidrug-resistant (MDR) organisms. For MDR-bacteria, common risk factors include long-term care facility residence, recent hospital admission, previous broad-spectrum antimicrobial use, known colonisation, and recent travel to high prevalence areas.[11,12,37] Antifungal-tolerant and drug-resistant fungal infections are an emerging concern in ICU with risk factors including known colonisation, long-term suppressive or prophylactic antifungal use, and previous exposure to antifungal therapy (eg haematological, cystic fibrosis, prolonged ICU patients).[13,14]

Traditional Diagnostic Pathways

Traditional laboratory diagnostic pathways for bacterial and fungal infection rely upon culture-based approaches that can be supported by information from the clinical assessment, radiological investigations, and biomarkers. Figure 1 outlines common diagnostics that can support decision-making for bacterial and fungal infections. The figure highlights that diagnostic decision-making is never a single event. The physician must have a baseline understanding of the information provided by specific diagnostic tests and the confidence with which this information can be interpreted. Generally, diagnostics can be used to support commencement, targeting, individualisation, and cessation of antimicrobial therapy. Table 2 summarises the strengths and weaknesses of individual diagnostic modalities at each stage in the decision-making pathway.

It is important to consider the influence that a diagnostic test may have at different stages of decision-making.[38] Ensuring the appropriate use of diagnostic investigations helps to ensure that optimal treatment decisions are made by providing reliable and correct information. This concept is a key component of diagnostic stewardship and is important in ensuring that the diagnostic laboratory can optimally support clinical decision-making.[39] This in-part relies on the requesting physician having knowledge of a test's sensitivity, specificity, and predictive values to ensure that its result can be appropriately interpreted and applied to the wider decision-making context.[40]

Advances in Diagnostics

For more than 100 years, microbiological diagnostics have mainly relied upon culture-based approaches to the identification and phenotypic characterisation of microorganisms (Figure 2).[41] Culture-based diagnostics provide a phenotypic antimicrobial susceptibility profile that allows the targeted prescription of antimicrobials with a high probability of success based on organism, drug pharmacokinetic/pharmacodynamic (PK/PD), and host factors.[42] Traditional culture-based approaches are associated with slow turnaround times, limited sensitivity, and are open to variation between laboratories. This means that often the organism's identity and antimicrobial susceptibility report will

Table 1 Risk Factors for the Development of Bacterial and Fungal Infections in the Intensive Care Unit

Diagnosis	Intrinsic Factors	Modifiable Factors	References
Candida blood stream infection	• Colonisation with *Candida* spp. • Diabetes mellitus • Gastrointestinal perforation • Older age (>65 years) • Pancreatitis • Sepsis/severe illness • Haematological/solid organ malignancy • Liver failure/cirrhosis • Gestational age (neonates) • Low APGAR score	• Dialysis • Systemic broad-spectrum antibiotic use • Central venous catheter • Corticosteroids & immunosuppression • Recent gastrointestinal surgery • Left ventricular assist device use • Long-term stay in the ICU • Prolonged mechanical ventilation • Total parenteral nutrition • Extracorporeal membrane oxygenation (ECMO) • Intravenous drug use	[6,61,97]
Invasive aspergillosis	• Prolonged or severe neutropaenia • Haematological malignancy • Severe illness • Trauma and burns • Underlying respiratory illness (eg cystic fibrosis) • Diabetes mellitus • Cardiovascular disease • Severe influenza • Severe COVID-19 • Defects in cell mediated immunity • Polymorphisms within pentraxin-3, TLR-3, TLR-4, and dectin-1	• Systemic corticosteroid and other immunosuppression use. • Chemotherapy • Haemopoietic stem cell transplantation (allogenic) • Chimeric antigen receptor T-cell therapy • Solid organ transplantation • Graft versus host disease • Immunotherapy (eg tyrosine kinase inhibitors and TNF-α inhibitors) • Prolonged ICU admission	[98]
Mucormycosis	• Poorly controlled diabetes mellitus • Metabolic acidosis • Prolonged or severe neutropaenia • Trauma and burns • Haematological malignancy • Severe COVD-19	• Systemic corticosteroid use • Haemopoietic stem cell transplant • Organ transplant • Deferoxamine therapy (iron chelation therapy) • Malnourishment • Intravenous drug use	[99]
Pneumocystis pneumonia	• Inherited immunodeficiency • Acquired immunodeficiency (HIV/AIDS)	• Immunosuppression (eg corticosteroids)	[100]
Drug-resistant/tolerant fungal infection	• Cystic fibrosis • Haematological/oncological malignancy • Critically ill patients • Intra-abdominal Candida infection	• Widespread prophylactic antifungal therapy • Widespread empiric antifungal therapy	[13,14]
Ventilator/hospital-acquired pneumonia	• Male gender • Older age • Pre-existing pulmonary disease • Coma/low GCS • Burns • Acquired immunodeficiency syndrome (AIDS) • Head trauma • Multiple-organ system failure	• Prior antimicrobial use • Mechanical ventilation • Neurosurgery • Intracranial pressure monitoring • Reintubation • Movement outside of the ICU	[101,102]
Blood stream infection	• High severity of illness • Liver disease • Surgical presentation	• Invasive devices (eg CVC) • Invasive procedures • Surgery during admission	[103]
Surgical site infection	• Colonisation with pathogenic organisms (eg *Staphylococcus aureus*) • Increasing age • Comorbidities (diabetes mellitus, obesity)	• Surgical procedure • Antimicrobial prophylaxis • Operating theatre specifications	[103]
Urinary Tract Infection	• High severity of illness	• Emergency catheter placement	[104]

(*Continued*)

Table 1 (Continued).

Diagnosis	Intrinsic Factors	Modifiable Factors	References
Multidrug-resistant bacteria	• Prior colonisation with MDR-pathogen • Long-term care requirements/hospitalisation • Severity of illness • Chronic respiratory disease • Cardiovascular diseases	• Prior antimicrobial exposure • Prolonged ICU stay (>7 days) • Mechanical ventilation/tracheostomy	[37]

Abbreviations: Spp, species; APGAR, appearance, pulse, grimace, activity, and respiration score; ICU, intensive care unit; TLR, toll-like receptor; TNF, tumour necrosis factor; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; GCS, Glasgow coma scale; CVC, central venous catheter.

not be available for 48–72 hours after a sample has been collected.[41] This leads to delays in the delivery of targeted and individualised therapy and provides a window of inappropriate therapy, whether wrong spectrum or unnecessarily broad.

Recent technological developments have aimed to reduce the turnaround-time of organism identification and susceptibility reporting. This includes improving the collection and delivery of samples to the microbiology laboratory,[43] the development of rapid antimicrobial susceptibility (AST) methodology,[44,45] and adoption of new technology for organism identification and AMR detection.[46,47]

The uptake of Matrix-Assisted Laser Desorption/Ionization – Time of Flight Mass Spectrometry (MALDI-TOF MS) is an example of technology that can facilitate rapid turn-around in organism identification and in certain cases the detection of antimicrobial resistance such as differentiation of methicillin susceptible from methicillin-resistant *Staphylococcus aureus*.[48–51] Turn-around time can be shortened further using MALDI-TOF MS through direct from sample identification protocols, which have demonstrated reasonable levels of sensitivity and specificity and allow quicker time to organism identification and thus targeted antimicrobial therapy.[49]

The development of molecular diagnostic tools provides an additional diagnostic modality that can support optimal antimicrobial decision-making for infection management in the ICU. Molecular diagnostics aim to bypass the culture-step in the diagnostic pathway facilitating rapid organism detection and identification directly from clinical specimens. Molecular diagnostics can also provide a mechanism for detection of known genotypic antimicrobial resistance.[52,53] Near-patient testing allows the deployment of molecular sample-to-answer platforms within the ICU environment and

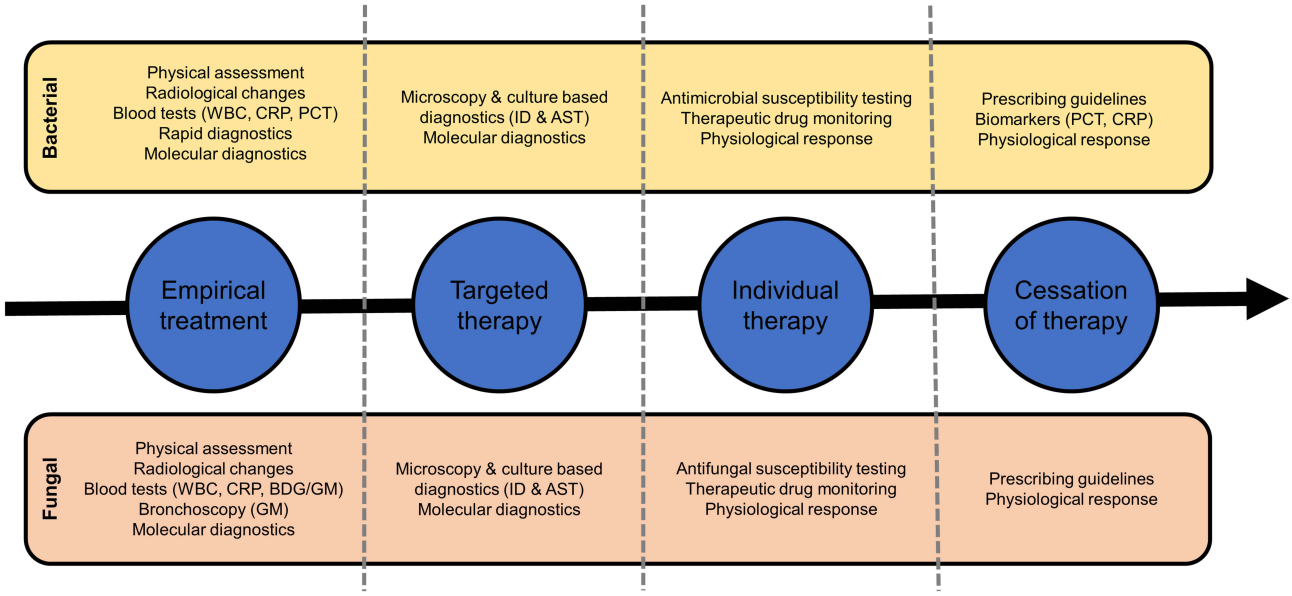

Figure 1 Common factors that influence antimicrobial decision-making at different steps in the pathway.
Abbreviations: WBC, white blood cell count; CRP, C-reactive protein; PCT, procalcitonin; ID, organism identification; AST, antimicrobial susceptibility testing; BDG, beta-D-glucan; GM, galactomannan.

Table 2 Common Diagnostics Used to Support Antimicrobial Decision-Making for Bacterial and Fungal Infections

Diagnostic	Characteristics	Diagnostic Use in Antimicrobial Decision-Making			
		Empiric Treatment	Targeted Therapy	Optimisation	Cessation
Blood culture (bacterial)[43]	Diagnosis improved by multiple sets*: • 20mL; 65–76% sensitivity • 40mL; 80–89% sensitivity • 60mL; 95–98% sensitivity	• N/A	• Targeted antimicrobial selection. • Known phenotype of infective organism.	• MIC guided dosing	• Facilitates evidence- based duration of therapy
Bacterial PCR[105]	Multiplex PCR: • Greater level of detection of organisms c.f. bacterial culture • Antimicrobial resistance gene identification	• Depending on turnaround time, may allow for delayed commencement of therapy pending results	• Earlier switch to targeted treatment (de-escalation) • Rule-in/rule-out organism presence.	• N/A	• N/A
Procalcitonin[106,107]	Diagnosis of bacterial infection: • Sensitivity 88% • Specificity 81%	• Differentiation of bacterial versus viral infection.	• N/A	• N/A	• Can reduce antibiotic utilisation without impact on infection-related outcomes
C-reactive protein[107–110]	Diagnosis of bacterial infection: • Sensitivity 75% • Specificity 67%	• Can support diagnosis of bacterial infection	• N/A	• Linkage to drug exposure may facilitate in-vivo estimation of antimicrobial pharmacodynamics	• Can shorten the duration of antimicrobial therapy without impact on infection-related outcomes
Blood culture (fungal)[111]	Diagnosis: • Positive in 50% cases of disseminated candidiasis	• N/A	• Targeted selection of antimicrobial therapy. • Known phenotype of infective organism.	• MIC guided dosing	• Facilitates evidence-based duration of therapy
Galactomannan[112–114]	Galactomannan on BAL • Sensitivity 82–89% • Specificity 96–99%	• Depending on turnaround time, may allow for delayed commencement of therapy	• Can support diagnosis and targeted treatment.	• Linkage to drug exposure may support in-vivo estimation of antimicrobial pharmacodynamics	• N/A

Beta-D-glucan[115]	• Sensitivity: 75% • Specificity: 85% • Poor PPV, good NPV • Prone to false positives • Negative in mucor and cryptococcal infection	• Can support decision-making around diagnosis of invasive fungal infection.	• N/A	• N/A	• Unclear benefit to supporting cessation of therapy.
Fungal PCR[111]	Candida PCR - Proven, probable, or possible Candidiasis: • Sensitivity 73% • Specificity 95% Higher sensitivity observed with blood culture. Aspergillus PCR: • Sensitivity 80.5% • Specificity 78.5% Syndromic multiplex panels available for positive blood cultures. Rapid ID with high sensitivity/specificity.	• Depending on turnaround time, may allow for delayed commencement of therapy.	• Can support diagnosis and targeted treatment.	• Emerging antifungal resistance gene marker detection available (eg CYP51A resistance)	• N/A
T2 Candida panel[116]	With positive blood culture: • Sensitivity 91% • Specificity 99% Low PPV in low prevalence settings (15–31% when prevalence <1%).	• N/A	• Organism identification	• No susceptibility data reported.	• Evidence-based duration based on diagnosis.

Notes: *Blood culture bottles typically collect 10mL per bottle, therefore 20mL per set (aerobic and anaerobic).
Abbreviations: N/A, not applicable; MIC, minimum inhibitory concentration; PCR, polymerase chain reaction; c.f., compared for; PPV, positive predictive value; NPV, negative predictive value; ID, identification; CYP, cytochrome P45.

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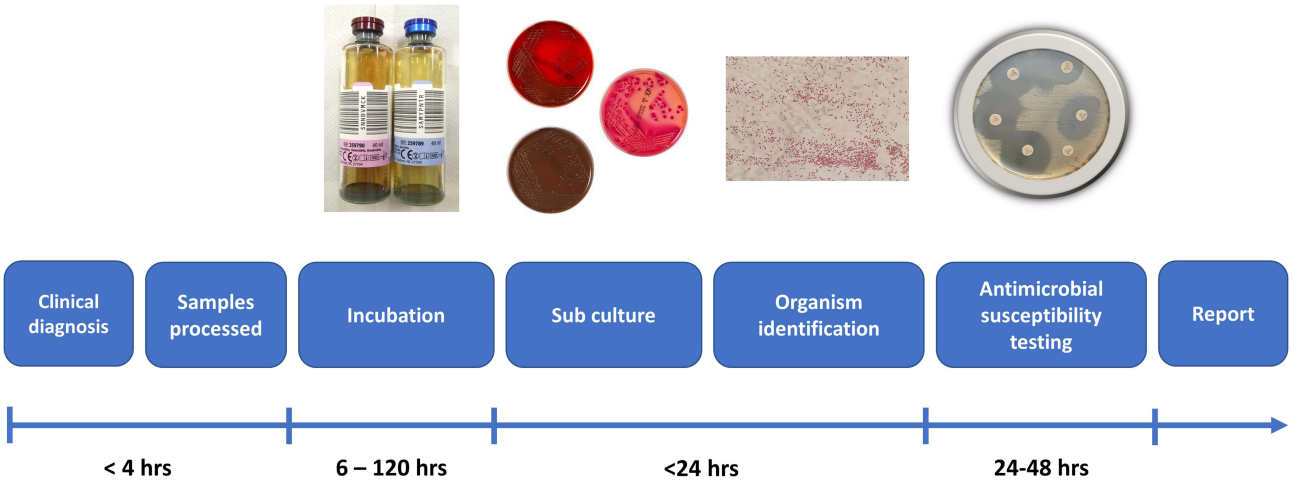

Figure 2 Traditional turn around time for culture-based diagnostics for blood cultures. *Turn around times referenced in this figure are adpated from from the UK SMI B 37: investigation of blood cultures (for organisms other than Mycobacterium species) 2022* https://www.gov.uk/government/publications/smi-b-37-investigation-of-blood-cultures-for-organisms-other-than-mycobacterium-species.
Abbreviation: AST, antimicrobial susceptibility testing.

can reduce time to organism identification and targeted antimicrobial therapy by around 24 hours.[54] To date, there has been a paucity of clinical trial data to support the application of molecular diagnostics. Where clinical trials have been performed, these have often failed to define appropriate outcome measures based on the likely impact on decision-making of the diagnostics being evaluated.[55] One example was a multi-centre randomised control trial of a respiratory multiplex-PCR platform linked to procalcitonin for the diagnosis of bacterial infections in patients admitted to the ICU with COVID-19.[56] This trial failed to demonstrate an impact of antibiotic prescribing but did demonstrate the improved sensitivity of such non-culture-based approaches for organism identification in populations with high rates of empiric antimicrobial prescribing prior to microbiological sampling.[56] Within this study, bacterial identification using multiplex-PCR was twice as high in the context of most patient (83%) receiving empiric antimicrobial therapy prior to microbiological sampling.[56]

Rapid AST can be performed for positive blood cultures using standard laboratory approaches or automated systems.[44,45,47] In current randomised control trials, these tools have demonstrated improved antimicrobial stewardship targets (both reduced time to effective therapy and reduced inappropriate treatment) but failed to demonstrate improvements in clinical outcomes including mortality.[57–59] For example, one study randomised positive blood cultures from patients with Gram-negative bacteraemia to undergo conventional versus rapid AST testing using an automated commercial method with a primary end point of time to narrowest effective therapy.[59] Rapid AST did not impact time to narrowest effective therapy but did significantly decrease time to oral antimicrobial switch and shortened length of hospital stay by two days.[59]

Management of Bacterial and Fungal Infection in the ICU

Initiation of early and appropriate antimicrobial therapy as part of a bundle of interventions is one of the most effective means of improving clinical outcomes for patients with secondary bacterial or fungal infection in the ICU.[32] Table 3 summarises the prevalence of common infective syndromes in the ICU and highlights examples of available international guidelines for their management.

When managing infection in the ICU, it is important to consider host, antimicrobial, and organism factors that can influence the outcome of treatment.[60] The presumed site of infection may require specific considerations (Table 3), such as line removal or source control, and the nature of the organism and its phenotype can play an important role in antimicrobial selection and duration of treatment. Critically ill patients will often have highly variable pharmacokinetics

Table 3 Prevalence, Common Causative Organisms, and Treatment Recommendations for Common Infective Syndromes Diagnosed in Intensive Care Patients

Infectious Syndrome	Proportion of ICU Infective Syndromes[2]	Common Pathogens	Special Considerations	Treatment Recommendations
Ventilator/hospital-acquired pneumonia	60%	GN: Enterobacterales, *Pseudomonas aeruginosa, Acinetobacter spp., Stenotrophomonas maltophilia* GP: *Staphylococcus aureus, Streptococcus spp.* Fungi: *Aspergillus spp.*, other moulds	GN: ESBL-production, AmpC-derepression, Carbapenemase-production GP: *MRSA, VRE*, toxin production	*ERS/ESICM/ESCMID/ALAT*[117] *IDSA/ATS*[118] *Chinese guidelines*[119] *South African Thoracic Society*[120]
Intra-abdominal infection	18%	GN: Enterobacterales GP: *Streptococcus milleri, Enterococcus spp.* Fungi: *Candida spp.*	Source control GN: ESBL-production, AmpC-derepression, Carbapenemase-production GP: *MRSA, VRE*, toxin production	*WSES/GAIS/SOS-E/WSIS/AAST*[121] *IDSA*[122] *Surgical infection society*[123]
Blood stream infection	15%	GP: *Staphylococcus aureus, Streptococcus spp., Enterococcus spp.* GN: Enterobacterales, *Pseudomonas aeruginosa, Acinetobacter spp.* Fungi: *Candida spp. Cryptococcus spp.*, Other less common yeasts, *Fusarium spp*	Catheter associated (CLASBI) Duration of intravenous antimicrobials GN: ESBL-production, AmpC-derepression, Carbapenemase-production GP: *MRSA, VRE*, toxin production	*IDSA*[124] *JAID/JSC guidelines*[125]
Urinary tract	Genitourinary 11% Kidney 3%	GN: Enterobacterales Fungi: *Candida spp.*	Source control Catheter associated GN: ESBL-production, AmpC-derepression, Carbapenemase-production	*CDC*[126] *NICE*[127]
Skin and soft tissue	6%	GP: *Staphylococcus aureus, Streptococcus spp.* GN: Enterobacterales Fungi: Mucoraceous moulds	GP: *MRSA, VRE*, toxin production	*WSES/SIS-E*[128] *IDSA*[129]

Abbreviations: GN, Gram-negative; GP, Gram-positive; Spp, species; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum beta-lactamase; VRE, vancomycin-resistant enterococcus.

(PK), making dose optimisation challenging. Environmental factors often mean that organisms with higher levels of a drug tolerance/resistance are also present, making selection and optimisation of antimicrobial therapy difficult.[11,12] It is important to have knowledge of local epidemiology to ensure that optimal empiric treatment decisions are made and antimicrobial pharmacodynamics (PD) optimised. Linking antimicrobial decision-making into the holistic management of infection in the ICU is vital, including fluid resuscitation, haemodynamic management, ventilation, and consideration of additional therapeutic interventions including blood sugar control, corticosteroids, and restrictive transfusion strategies.[32]

Empiric Antimicrobial Therapy

Empirical antimicrobial selection aims to cover common causative organisms for an infection whilst awaiting definitive results to facilitate targeted treatment to be delivered. Empiric treatment should aim to provide an appropriate antimicrobial spectrum for common causative organisms and prevalent drug-resistant phenotypes. It should select agents with appropriate PK/PD properties for the suspected site and severity of infection.

A major challenge in the ICU is the greater prevalence of drug-resistant infections and the often potential severe consequences of selecting an inappropriate empiric treatment regimen.[11,12] This means that broad-spectrum antimicrobials with anti-pseudomonal spectrum are often required. In areas with high prevalence of MRSA, glycopeptides are often co-administered empirically.[32] For suspected fungal infection, the commencement of echinocandin therapy is recommended for suspected candidaemia with amphotericin-B often used empirically for invasive mould infections.[13,61] The diagnosis of infection often requires consideration of numerous factors summarised in Figure 1. Based on a syndromic diagnosis (eg respiratory tract, urinary tract, skin-soft-tissue infection) guidelines are developed taking

into account common causative organisms and local resistance patterns. Table 3 summarises common causative organisms, special considerations, and national/international guidance that is often taken into consideration for common syndromic diagnoses in the ICU.

In addition to ensuring an appropriate spectrum of therapy is delivered as part of empiric treatment, optimisation of drug delivery must also be considered.[60] Critical illness is a major cause of PK/PD variation that is associated with increased risk of mortality, especially in sepsis.[62] To address observed variability in antimicrobial PK/PD, prolonged or continuous infusion of beta-lactam and glycopeptide antibiotics is often recommended to ensure optimised targeted attainment.[63,64]

Targeted/Individualised Antimicrobial Therapy

In septic shock, the administration of antimicrobial therapy within an hour of recognition has been suggested to be important to reduce mortality.[32] In patients without shock, current guidelines support commencement of therapy within up to 3 hours of recognition.[32] Whilst delaying empiric treatment decisions until culture-based diagnostic results are available is often not possible in critically ill patients with bacterial or fungal infection, developments in point-of-care molecular diagnostic platforms may provide a greater abundance of information with which to deliver targeted therapy sooner.[65–67] For example, Banerjee et al demonstrated that linkage of a multiplex molecular diagnostic facilitated rapid organism identification, targeted therapy, and more rapid de-escalation of treatment when linked with antimicrobial stewardship support for patients with positive blood cultures.[54]

Once culture-based diagnostics provide appropriate organism and susceptibility results, switching from broad-spectrum empiric therapy to targeted treatment can reduce potential adverse events for patients and reduce the propagation of AMR.[68] Despite a lack of randomised control trial data supporting the safety of early de-escalation of antimicrobial therapy in sepsis,[69] observational data have demonstrated that early de-escalation is safe and does not impact on mortality.[70] Furthermore, a large retrospective analysis of over 17,000 patients admitted to hospitals in the USA with sepsis identified an increased risk of mortality associated with unnecessarily broad antimicrobial therapy within this cohort.[9]

The role of therapeutic drug monitoring (TDM) to ensure optimal drug exposure in critically ill patients is now recognised. Guidance on antimicrobial TDM in critically ill patients is emerging from beta-lactam antibiotics, and agents with narrow therapeutic windows, such as vancomycin and linezolid.[71] The overall impact of antimicrobial and antifungal TDM on patient outcomes is still to be determined,[72] but it is likely to be an important consideration to ensure that optimal PK/PD targets are achieved in patients with highly variable pharmacokinetics.

The Importance of Source Control and Other Non-Antimicrobial Factors

In addition to optimal antimicrobial selection, infection management must ensure adequate source control where possible.[73–75] The objective of source control is to remove any source of persistent infection, prevent ongoing contamination, and restore pre-morbid function and anatomy where possible.[74] Source control can be divided into three broad categories: drainage of collections or abscesses, debridement or removal of infected devices, and definitive control measures.[75] Current guidelines recommend prompt performance of source control, when safe to do so, to ensure optimal outcomes for individual patients.[32]

Within the ICU, source control is often focussed on reducing or eliminating invasive interventions that are no longer required. Whilst routine replacement of central venous catheters has not been shown to reduce infection risk and is not recommended,[76] such devices should be reviewed regularly and removed when they are no longer required or replaced if there is suspicion of catheter associated infection.[76,77] If infection is suspected, catheters should be placed at a new site and re-wiring the old line should be avoided. Daily sedation holds and spontaneous breathing trials have been suggested as a means to reduce the need for mechanical ventilation,[78] although this approach has not been consistently found to reduce the duration of mechanical ventilation.[79,80]

Infection Prevention in the ICU

A high proportion of secondary bacterial and fungal infections in the ICU are preventable.[1] Table 4 summarises key infection prevention measures that can be applied generally and to different syndromic settings within the ICU.

Infection prevention in the ICU relies on a multi-modal approach that encompasses hand hygiene, environmental hygiene, screening and isolation approaches, surveillance, antimicrobial stewardship, and implementation of specific patient safety guidelines and bundles.[81] Hand hygiene is probably the most important infection prevention intervention. There is robust evidence that links rates of hand hygiene compliance with incidence of nosocomial infection.[82,83] The aim of hand hygiene is to reduce transient micro-organisms that are acquired by healthcare staff during the course of their

Table 4 Summary of Common Infection Prevention and Control Approaches in the Intensive Care Unit

Area	Measure	Evidence	Reference
General infection prevention and control measures			
	Hand hygiene	• Improved compliance with hand hygiene is associated with direct reductions in healthcare-associated infections. • No clear evidence around optimal strategy for hand hygiene. • Compliance often declines with time.	[82,83]
	Environmental hygiene	• Environmental cleaning measures lead to reductions in patient colonisation or healthcare-associated infections. • Without cleaning measures, a patient is 150–500% more likely to acquire a pathogen that a prior room occupant was colonised with.	[130]
	Ventilation	• Ventilation requirements for the bed space should be appropriate to both the immunological status of the patient and sufficient to mitigate risk of airborne transmission for any pathogens the patient may have.	[131]
	Screening & isolation	• Where there is evidence that colonisation increases the risk of infection, as with *MRSA*, screening with suppression therapy or isolation can be of benefit. • Screening and isolation can be used in outbreak situations to terminate the chain of infection.	[132]
	Selective digestive decontamination	• Reduces the rate of bacteraemia and *VAP* in mechanically ventilated patients. • No evidence of emergence of drug-resistance during treatment. • Limited high-quality evidence of the ecological impact of long-term *SDD* and its effectiveness in areas with high rates of *MDRO* infections.	[89]
	Surveillance	• Hospital-based surveillance when linked to national surveillance systems is associated with overall reductions in *HCAI*.	[81]
	Antimicrobial stewardship	• Antimicrobial stewardship interventions can significantly reduce the selection and propagation of drug-resistant infections. • Adherence to antimicrobial stewardship policy can reduce *HCAI*, drug-resistant infections, and complications like *C. difficile* infection.	[68]
	Patient safety guidelines/bundles	• Care bundles contain 3–5 evidence-informed practices that must be delivered collectively and consistently with the aim of improving patient outcomes for a certain aspect of care. • Care bundles for specific IPC challenges are superior to the sum individual interventions included (see below)	[133]

(*Continued*)

Table 4 (Continued).

Area	Measure	Evidence	Reference
Ventilator/hospital-acquired infection		• Use of bundled approaches (eg "100K Lives Campaign") has demonstrated significant reduction in VAP incidence. • Core bundle components include elevating the head of the bed (30–45°), daily sedation and assessment for extubation, subglottic secretion drainage, avoiding frequent ventilatory circuit changes. Additional interventions often added to bundles include hand hygiene, oral care with chlorhexidine, education and training, cuff pressure control, enteral feeding, and avoidance of stress ulcer prophylaxis where possible.	[94,95]
Central line associated blood stream infections		• Use of bundled approaches (eg "Matching Michigan") comprising standardised technical and non-technical interventions significantly reduces CLASBI. • Bundled approaches use technical standardisation including hand hygiene, PPE use, skin preparation/asepsis, maximal sterile precautions, optimal insertion site selection, and daily central venous catheter (CVC) maintenance/line care. Non-technical aspects include minimal levels of training, audit and feedback, and communication skills.	[92,93]
Surgical site infection		• Peri-operative care bundles lead to observed reductions in *SSI*. These tend to be more effective when interventions with higher levels of evidence are present. • Bundles incorporate pre-operative preparation (eg nasal decolonisation and hair removal), intra-operative (eg hand hygiene, sterile drapes, skin preparation, antimicrobial prophylaxis), and post-operative (eg dressings, cleaning, and support from specialist wound care services) interventions.	[134,135]
Catheter associated urinary tract infection		• Interventions that focus on reducing unnecessary insertion and prolonged duration of urinary catheterisation can reduce *CAUTI* incidence significantly. • Bundled interventions focus on selection of appropriate patients requiring urinary catheterisation, aseptic insertion, and routine maintenance once inserted. • Surveillance and reporting with audit and feedback can play an important role in supporting adherence to best practice.	[126,136,137]

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; SDD, selective digestive decontamination; MDRO, multidrug-resistant organism; VAP, ventilator associated pneumonia; HCAI, healthcare associated infection; CLASBI, central line associated blood stream infection; SSI, surgical site infection; CAUTI, catheter-associated urinary tract infection.

working day. These transient organisms are easily transmitted on contact with patients and therefore are a primary route for the spread of nosocomial pathogens.[82,83] The use of alcohol-based hand gels and soap and water washing is the mainstay of hand hygiene. An example of the impact of breakdown in hand hygiene measures within the ICU was observed globally during the COVID-19 pandemic, with outbreaks of organisms such as *Corynebacterium striatum* observed following breakdown in hand washing and glove changes between patients due to adaptions in personal protective equipment (PPE) policy to protect healthcare workers.[84]

The selection of transmission-based precautions to reduce the transmission of drug-resistant bacteria (eg MRSA and GRE) is often controversial. Randomised control trial data have failed to demonstrate significant reductions in transmission through the implementation of barrier precautions in colonised patients.[85] Hand hygiene adherence is likely to have the greatest overall impact in reducing transmission of drug-resistant organisms, such as GRE.[86] For organisms that can have persistence in the environment, such as *Clostridioides difficile* spores, hand hygiene, environmental control, and appropriate barrier precautions can reduce transmission to other patients.[87]

Surveillance is an ongoing challenge that can be performed at local, regional, and national levels. Within England and the United Kingdom, reporting of certain infections such as MRSA blood stream infections and central-line associated blood stream infections are mandatory and can help to drive a culture of safety and accountability. The screening and reporting of AMR can help identify outbreaks and inform development of local antimicrobial policy.[88]

Selective Decontamination of the Digestive Tract (SDD) has been proposed to reduce the risk of ventilator-associated pneumonia in patients requiring invasive mechanical ventilation.[89,90] SDD is the application of topical nonabsorbable antibiotics and antifungal agents to the upper gastrointestinal tract combined with a short course of intravenous antibiotics. A recent large randomised trial of SDD showed that although SDD did not reduce mortality there was a reduction in the rate of bacteraemia (5.6% vs 8.1%) and the number of drug-resistant infections (23.1% vs 34.6%).[91] A subsequent meta-analysis of studies of SDD has shown that SDD may reduce mortality, VAP, and ICU-acquired bacteraemia.[89] Whilst observational data in areas with relatively low prevalence of drug-resistant infections suggest that SDD does not promote the development of AMR, high-quality data on the unintended consequences of SDD at an ecological level remains to be established.[90]

Within hospitals, including critical care departments, IPC policy aims to implement multi-modal interventions that facilitate safe, effective, and high-quality care for patients. In addition to general IPC measures, care bundles are recognised to reduce infection risk for a range of nosocomial infections (Table 4). Care bundles are a collection of interventions that implemented together have a greater impact than the sum of individual interventions used within it. The "Matching Michigan" campaign for the prevention of central line associated blood stream infections[92,93] and '100K lives campaign' for ventilator associated pneumonia[94,95] are examples of bundled interventions that have significantly reduced rates of infection following their implementation. The Surviving Sepsis Campaign is an example of a bundled intervention that has been demonstrated to reduce mortality in patients with sepsis.[96]

Conclusion

Bacterial and fungal infection in ICU patients are important events that must be considered by all those involved in the care of critically ill patients. A large proportion of infections are preventable through the implementation and adherence to multi-modal IPC policies. The diagnosis of infection can be complex and evolve over time as additional information becomes available. The advent of molecular diagnostics and rapid methods for determination of AST are providing us with information on organism characteristics sooner. This must be applied to a wider decision-making context to ensure that these new technologies have significant benefit for patients.

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