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REVIEW ARTICLE

Infections in Critically Ill Children

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Abstract
Health care–associated infections (HAI) directly influence the survival of children in pediatric intensive care units (PICU), the most common being central line–associated bloodstream infection (CLABSI) 25–30%, followed by ventilator-associated pneumonia (VAP) 20–25%, and others such as catheter-associated urinary tract infection (CAUTI) 15%, surgical site infection (SSI) 11%. HAIs complicate the course of the disease, especially the critical one, thereby increasing the mortality, morbidity, length of hospital stay, and cost. The incidence of HAI in Western countries is 6.1–15.1% and in India, it is 10.5 to 19.5%. The advances in healthcare practices have reduced the incidence of HAIs in the recent years which is possible due to strict asepsis, hand hygiene practices, surveillance of infections, antibiotic stewardship, and adherence to bundled care. The burden of drug resistance and emerging infections are increasing with limited antibiotics in hand, is still a dreadful threat. The most common manifestation of HAIs is fever in PICU, hence the appropriate targeted search to identify the cause of fever should be done. Proper isolation practices, judicious handling of devices, regular microbiologic audit, local spectrum of organisms, identification of barriers in compliance of hand hygiene practices, appropriate education and training, all put together in an efficient and sustained system improves patient outcome.

Keywords Hospital-acquired infections · Resistant organisms · Central line–associated bloodstream infections · Ventilator-associated pneumonia · Antibiotic stewardship

Introduction

In recent years, there has been a tremendous advancement in medicine and health care facilities, which has led to an increase in the infections acquired from hospitals while being nursed. As the advances in medicine increase, the burden of resistant organisms becomes inevitable. Hospital-acquired infections complicate the course of the disease, especially the critical one, thereby increasing the mortality, morbidity, length of hospital stay, and cost [1]. According to the Centres for Disease Control and Prevention (CDC), a hospital-acquired infection (HAI) is a localized or systemic condition secondary to the infection that was not present at the time of admission to the health care facility [2]. The incidence of HAI in Western countries is 6.1–15.1% [3, 4], and in India, it is 10.5 to 19.5% [3, 5]. The most common HAIs encountered in the pediatric intensive care units (PICU) are central line–associated bloodstream infection (CLABSI) 25–30%, ventilator-associated pneumonia (VAP) 20–25%, catheter-associated urinary tract infection (CAUTI) 15% [3], and surgical site infection (SSI) 11% [6]. Refined health care and compliance with protocols have led to a decrease in HAIs in recent decades. In this review article, the various health care–associated infections that are frequently encountered and managed in PICUs are discussed.

Definitions

Central Line-Associated Bloodstream Infection (CLABSI): A primary bloodstream infection confirmed by blood culture or non-culture-based microbiologic testing, and a Central Venous Catheter (CVC) has been in place for more than 2 calendar days and the infection is not attributable to another site [7].

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Ventilator-Associated Condition (VAC): ≥ 2 calendar days of stable or decreasing daily minimum PEEP or FiO_2, followed by a rise in PEEP ≥ 3 cm H_2O or a rise in FiO_2 ≥ 20 points sustained for ≥ 2 d [8].

Infection-Related VAC (IVAC): VAC plus temperature > 38°C or < 36°C or leukocytosis or leukopenia and one or more new antibiotics continued for ≥ 4 d within 2 d before or after VAC onset on or after 3 calendar days of mechanical ventilation [8].

Possible Ventilator-Associated Pneumonia (PVAP): On or after 3 calendar days of mechanical ventilation and 2 calendar days before or after the onset of worsening oxygenation, one of the following criteria should be met.

1. Positive culture quantitative/semiquantitative with/without purulent secretions from endotracheal aspirate (≥ 10^5 CFU/mL), BAL (bronchioalveolar lavage) (≥ 10^4 CFU/mL), lung tissue (≥ 10^4 CFU/mL), or protected specimen brush (≥ 10^3 CFU/mL).
2. Purulent respiratory secretions + organism identified from one of the following—sputum, ET aspirate, BAL, lung tissue, or protected specimen brush.
3. One of the following positive tests

- Organism identified in pleural fluid within 24 h of chest tube placement.
- Lung histopathology defined as (1) abscess formation or foci of consolidation with intense neutrophil accumulation, (2) evidence of lung parenchyma evasion by fungi, (3) evidence of infection with viral pathogen.
- Diagnostic test for legionella.
- Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus (RSV), adenovirus, parainfluenza virus, rhinovirus, coronavirus, and human metapneumovirus [8].

Catheter-Associated Urinary Tract Infection (CAUTI): UTI occurs when an indwelling urinary catheter has been in place for more than two consecutive days in an inpatient location or 1 d after the removal of indwelling catheter.

Associated with at least one of the signs and symptoms:

- Fever > 38.0°C, suprapubic tenderness, costovertebral angle pain, urinary urgency, increased urinary frequency, and dysuria.

Patient has a urine culture with no more than two species of organism identified, at least one of which is of bacterium of ≥ 10^5 CFU/mL [9].

Epidemiology

Central line–associated bloodstream infections (CLABSI) remain the first most common HAI [10–12] and the second most common is ventilator-associated pneumonia (VAP) [13]. The incidence of CLABSIs varied from 0.5 to 4.0 per 1000 catheter days in developed countries and 14–15 per 1000 catheter days in developing countries [12]. CLABSI among the HAIs carries a significant mortality risk of around 12–25% and morbidity in the form of longer duration of PICU stay [12]. VAP accounts for up to 20% of HAIs in different pediatric series and has a rate of 2.9–21.6 per 1000 ventilator days [14]. The incidence of VAP ranged from 17.5 to 32.5% in various Indian studies [15]. The mortality of VAP in pediatrics ranges from 21 to 42% in India [14]. Risk of CAUTI occurs at a rate of 3–10% per day of catheterization, and the incidence approaches 100% within 30 hospital days [9].

Nearly 40–80% of CLABSIs are caused by gram-positive organisms such as coagulase-negative staphylococci, *Staphylococcus aureus*, etc.; the other gram-negative organisms and candida constitute the rest [16, 17]. Pseudomonas is commonly seen in severe illnesses, neutropenia, or prior colonization as in cystic fibrosis. Candida is particularly associated with femoral catheterization, total parenteral nutrition (TPN), prolonged administration of broad-spectrum antibiotics, hematological malignancies, and solid organ or hematopoietic stem cell transplantation [12, 16]. Common pathogens responsible for VAP are aerobic gram-negative bacilli (45–100%) such as *Acinetobacter sp.*, *E. coli*, etc. [18]. In Indian PICUs, *Acinetobacter spp.* is an emerging pathogen. Among gram-positive organisms, MRSA is the major pathogen [19]. Organisms causing CAUTI are more resistant to antibiotics, and 3% of CAUTI patients are at risk of developing bacteremia. A patient who develops complicated CAUTI has an increased risk for hypertension and end-stage renal disease in later life. A National Healthcare Safety Network (NHSN) review listed that uropathogenic *E. coli* (UPEC) accounts for 23.9% of cases of CAUTI, followed by *Candida sp.* (17.8%), *Enterococcus sp.* (13.8%), and *Pseudomonas aeruginosa* (10.3%) [9]. According to the CDC's 2018 data [6], surgical site infection accounts for 11% of ICU deaths [6]. The rate of SSI depends on the type of surgery, such as 2.1, 3.3, 6.4, and 7.1 for every 1000 operations for clean, clean-contaminated, contaminated, and dirty surgery, respectively. The proportion of MRSA in SSI is increasing, from 12% to 2000 to 43.7% in 2010 [6].

Table 1 Modifiable and Non-modifiable risk factors of HAIs

	Modifiable	Non-modifiable
CLABSI [12, 41]	Prolonged hospitalization before central-line placement Total parenteral nutrition Extracorporeal life support Renal replacement therapy Multilumen catheters Type of CVC material Site and insertion techniques - handling Duration of indwelling catheter	Young age (especially newborn) Male gender Burns Genetic abnormality Immune deficiency
VAP [42]	Reintubation/Self-extubation Prolonged mechanical ventilation Supine position Previous antibiotic uses and bloodstream infection Use of steroids Use of gastric acid–modifying drugs Use of narcotics, neuromuscular agents Invasive procedures like bronchoscopy	Genetic syndrome Neurological impairment Immunodeficiency Airway malformations Congenital heart disease
CAUTI [20]	Duration of catheterization Breach in catheter sterility Chronic undernutrition	Chronic kidney disease Immune deficiency Fecal incontinence

CAUTI Catheter-associated urinary tract infection, *CLABSI* Central line–associated blood stream infection, *CVC* Central venous catheter, *HAI* Health care–associated infections, *VAP* Ventilator-associated pneumonia

Risk Factors

There are several factors that increase the incidence of HAIs. These factors are mostly modifiable and seldom non-modifiable; if precautions are taken accordingly, the rate of HAIs can be reduced, which is shown in Table 1.

Pathogenesis

Nontunneled catheters are the most commonly used catheters, which are inserted percutaneously and account for most CLABSIs. There are three main routes of contamination of the central line: skin migration of organisms along the external surface of the catheter into the bloodstream; hematogenous route from pre-existing infection or other sources such as VAP, CAUTI, etc.; and contaminated infusate [12, 17].

Intubation and mechanical ventilation increase the risk of VAP by 6–21-fold [18]. Intubation causes a breach in the natural barrier between the oropharynx and trachea, and facilitates microaspiration of oropharyngeal secretions containing colonized pathogens through the leakage of secretions around the endotracheal tube. Biofilm formation in the endotracheal tube makes it difficult to eradicate the organism. Other infrequent modes of entry are through inhalation or direct inoculation, macroaspiration from the stomach and hematogenous spread from other sites.

The CAUTI spread can be extraluminal and/or intraluminal [20]. The flushing mechanism of the urinary tract is circumvented by the catheter, and perineal and urethral flora can pass up into the bladder (i.e. extraluminally). An intraluminal infection is an ascending infection caused by the bacterial reflux from contaminated urine in the drainage bag. Closed drainage systems reduce the onset of infection by limiting the access of bacteria to the urine. Patients who were catheterized for short term (≤ 7 d) had 10–50% risk of biofilm formation; however, practically all patients who were catheterized long term (> 28 d) were found to have biofilm formation [9]. Infection at the site where surgery has taken place is surgical site infection. It can be superficially restricted to skin or can spread deep to involve organs and cause dysfunction. SSI can occur from endogenous or exogenous flora contamination of surgical site [6].

Prevention Strategies

Asepsis, hand hygiene, and bundled approach reduce the rate and number of infections. It has to be implemented in every PICU, and adherence should be strictly maintained. The bundles are formulated based on several clinical trials including adult and pediatric population and expert opinions (Table 2).

Personal Protective Measures

Personal protective equipment consists of gloves, eye goggles, gowns, a face shield, and masks. They vary according to the type of infection. Hand hygiene should be done before wearing PPE. Gloves are worn while handling body fluids or while doing a sterile procedure; mask, eye or face protection in case splashes or sprays of body fluids are expected. N95 is worn in the case of an aerosol-generating procedure or in any infection that is transmitted from aerosols [21].

Isolation Practices

Patients are isolated according to the infectiousness of the organism because it can spread and threaten the safety of the patient, co-patients, and staff [21].

Contact Isolation: This is done for resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA),

Table 2 Prevention strategies

	Insertion bundle	Maintenance bundle
CLABSI [17]	- Strict asepsis - Use of 2% chlorhexidine skin preparations - Ultrasound guidance by an experienced provider (reduces the number of attempts) - Preferring the subclavian vein, when possible, for nontunnelled catheters - Prompt removal of any line when no longer required - Usage of a checklist	- Daily assessment of the need for the central line - Disinfection of the catheter hubs, injection ports, and connections before accessing the line - Change of gauze dressings every 2 d unless soiled, dampened, or loosened (CDC recommended) - Change of clear dressing every 7 d unless soiled, dampened, or loosened (CDC recommended) - Replacing administration sets other than sets used for lipids or blood products every 72–96 h - Replace tubing used to administer blood, blood products, or lipids within 24 h after initiation of infusion (CDC recommended) - Change caps no more often than 72 h and when the administration set is changed
VAP [8]	- Avoid invasive ventilation - Prefer noninvasive ventilation - Select appropriate tube size - Prefer cuffed endotracheal tubes - Maintain cuff pressure at 20 cm of H_2O	- Elevation of the head of bed in infants and children, so that upper torso remains at 30°–45° angle to the rest of body - Oral care in pediatric patients - wiping baby's gum twice with clean gauze or brushing teeth with paste > 2-y-old child - Minimize the duration of ventilation - Avoid unplanned extubations - Prevent condensation - Closed inline suctioning
CAUTI [43]	- Avoid unnecessary catheterization - Choose catheters of appropriate size - Use sterile items/equipment - Using chlorhexidine for cleaning - Insert catheter using strict aseptic nontouch technique - Antibiotic coated catheter - there is no evidence that it decreases symptomatic CAUTI, and therefore, they should not be used - Use closed drainage system - Secure catheter appropriately to prevent movement of urethra	- Review the need for the catheter on a daily basis and remove catheter promptly when no longer necessary - Do not break the closed drainage system. If urine specimen required, take specimen aseptically via the sampling port - Empty the bag every 8 h or when 2/3 full - Use a separate disinfected jug to collect urine from each bag; bladder irrigation or washout and instillation of antiseptics or antimicrobial agents do not prevent CAUTI, and therefore, should not be used for this purpose

CAUTI Catheter-associated urinary tract infection, *CDC* Centres for disease control and prevention, *CLABSI* Central line–associated blood stream infection, *VAP* Ventilator-associated pneumonia

Acinetobacter sp., vancomycin-resistant enterococcus (VRE), and carbapenem-resistant organisms.

Negative Pressure Isolation: The air pressure is lower than the pressure outside. It prevents pathogens from flowing outside into noncontaminant areas (keeps pathogen in). Highly infectious organisms, e.g., respiratory syncytial virus (RSV), multidrug-resistant (MDR), or extended drug–resistant tuberculosis (XDR-TB), etc.

Positive Pressure Isolation: The air pressure is higher than the pressure outside. It prevents pathogens from entering the patient airspace from outside (keeps pathogen out) and is helpful in immunocompromised patients.

Antibiotic Stewardship

Hospitals are the nidus for all emerging and resistant organisms, as they provide the setting that facilitates their genetic drift and shift. The unrestricted and erratic use of antibiotics has added fuel to this unyielding scenario. Hence, it is mandatory to have a written antibiotic policy in each and every hospital, and one should highly resist starting antibiotics in noninfective cases. As there are limited antibiotics and faster-evolving resistant organisms, survival becomes critical, and it solely depends on the responsibility of the physician. Empirical antibiotics should be narrowed to sensitive antibiotics based on culture and sensitivity. One should have a separate protocol-based approach to the frequently encountered organisms in one's hospital and should follow the WHO guidelines for antibiotic stewardship meticulously [22].

Table 3 Surveillance of HAIs [2, 23]

Infection window period (IWP)	Defined as the 7 d during which all site-specific infection criteria must be met. It includes the collection date of the first positive diagnostic test that is used as an element to meet the site-specific infection criterion, the 3 calendar days before and the 3 calendar days after
Date of event (DOA)	Date the first element used to meet an NHSN site-specific infection criterion occurs for the first time within the 7-d infection window period
Present on admission (POA)	If the date of event of the NHSN site-specific infection criterion occurs during the POA time period, which is defined as the day of admission to an inpatient location (calendar day 1), the 2 d before admission, and the calendar day after admission
Health care–associated infection (HAI)	Localized or systemic condition secondary to infection that was not present at the time of admission to the health care facility
Repeat infection time frame (RIIT)	Is a 14-d timeframe during which no new infections of the same type are reported
Secondary BSI attribution period	Is the period in which a blood specimen must be collected for a secondary bloodstream infection to be attributed to a primary site infection. This period includes the infection window period combined with the repeat infection timeframe (RIT). It is 14–17 d in length depending upon the date of event.
Pediatric VAEs (ventilator-associated events) (PedVAEs)	Patient has a baseline stability or improvement on ventilator, defined by ≥ 2 calendar days or decreasing daily minimum FiO_2 ≥ 0.25 or MAP values ≥ 4 cm of H_2O sustained for ≥ 2 d. The baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum MAP or FiO_2 that is maintained for > 1 h

NHSN National Healthcare Safety Network

Goals of Treatment

1. Initiating broad-spectrum empiric treatment at the suspicion of sepsis.
2. Choosing an appropriate antibiotic based on the risk of MDR organism in the patient and the local prevalence of the organism and pattern of resistance.
3. Review of antibiotics to stop after 48–72 h by clinical assessment and going through the culture-sensitivity report.
4. The optimization of antibiotics or switching to monotherapy by day 3–5.
5. Shortening the duration of therapy.
6. Using targeted therapy such as aerosolized therapy, intraventricular therapy, intrasynovial therapy, etc. to eradicate the organism faster.
7. Having a written antibiotic policy and compliance to the same in every hospital according to local antibiogram.
8. Cycling of antibiotics on regular basis.
9. Following aseptic measures and hand hygiene.
10. Following isolation practices in case of resistant or highly infectious organisms.

Surveillance Strategies (Table 3)

Definitions in surveillance are meant for quality improvement at the population level; they do not help in diagnosis or management at the bedside [2, 23].

Management

CLABSI: Whenever CLABSI is clinically suspected, the blood cultures are to be sent from all the ports along with a peripheral sample, and the empiric antibiotic therapy should be started promptly according to the local antibiogram and organisms encountered [24] (Table 4).

Salvage Therapy: Systemic therapy coupled with antimicrobial lock (heparin + high concentration of antimicrobial agent selected on susceptibility results) may be considered in hemodynamically stable chronic catheter use [24].

VAP: Though radiographic, clinical, and laboratory criteria are mandatory for suspicion as well as a definite diagnosis of VAP, they are neither sensitive nor specific [25]. The role of USG is emerging, but the data on its sensitivity and specificity are lacking [26]. The diagnosis is confirmed when a pathogen is identified in the lower respiratory sample obtained by blind endotracheal suction or bronchoalveolar lavage. The *Staphylococcus aureus* nasal PCR test has demonstrated a high negative predictive value for MRSA colonization in the patient population with a 10% prevalence of MRSA [27]. The respiratory viral panel and a PCR-based nasopharyngeal swab may be used during influenza season to identify the viral etiology of VAP where antibiotic therapy may not be necessary.

Risk factors for MDR VAP [28].

a) Prior intravenous antibiotic use within 90 d.
b) Septic shock at time of VAP.
c) Acute respiratory distress syndrome preceding VAP.
d) Acute renal replacement therapy prior to VAP onset.

Treatment of VAT (ventilator-associated tracheitis) is controversial, but its treatment reduces the chance of VAP. So, when VAT is treated, the duration of antibiotics is 3–5 d and for VAP, it is 7–10 d (Table 5).

Table 4 Empirical antimicrobial treatment in CLABSI

Scenario	Antibiotic of choice
Gram-positive coverage	
Usual gram-positive coverage with anti-staphylococcal cover in MSSA	Cloxacillin or cefazolin
MRSA prevalence	Vancomycin
MRSA with MIC > 2 mg/mL for vancomycin or vancomycin-resistant enterococci	Daptomycin
Gram-negative coverage	
Gram-negative coverage	3rd generation cephalosporins (ceftriaxone)
High risk for resistant organisms	β-lactam & β-lactamase inhibitor or combination of 4th generation cephalosporins or carbapenem with or without aminoglycoside
Neutropenia with immunosuppression Cystic fibrosis with prior colonization	Anti-pseudomonal coverage required
Candida suspicion	
Candida suspected	Echinocandin or fluconazole initial choice
Azole resistance or non-*Candida albicans* (*C. glabrata* or *C. krusei*)	Echinocandins (micafungin, caspofungin, anidulafungin)
Duration of therapy	
Complicated CLABSI - endocarditis or suppurative thrombosis or metastatic infection	4–6 wk
Uncomplicated CLABSI	*Staphylococcus aureus* -14 d CONS -7 d Enterococci and gram-negative bacilli -10–14 d Candida -14 d from last sterile culture

CLABSI Central line–associated blood stream infection, CONS Coagulase-negative staphylococcus, *MIC* Minimum inhibitory concentration, *MRSA* Methicillin-resistant *Staphylococcus aureus*, *MSSA* Methicillin-sensitive *Staphylococcus aureus*

Table 5 Empiric antimicrobial treatment in VAP

Scenario	Empiric regimen
Most cases	Cefepime or ceftazidime or meropenem
Sepsis or septic shock or necrotizing pneumonia	Vancomycin plus cefepime or ceftazidime or meropenem
MRSA colonization or prior MRSA infection	Vancomycin plus cefepime or ceftazidime or meropenem
Vancomycin-resistant cases	Linezolid
Allergy to penicillin and cephalosporin	Vancomycin plus aztreonam
Recent infection with MDR organism within 90 d	ESBL producer: meropenem

VAP Ventilator-associated pneumonia

CAUTI: Sterile suprapubic aspirate samples or clean, newly catheterized samples are sent for culture sensitivity, and the empirical gram-negative coverage is started and then tapered accordingly based on the antibiogram. The duration of treatment varies according to the clinical course and ranges from 5 to 14 d [29].

Skin and Soft Tissue Infections: Any skin and soft tissue infection should be addressed immediately as it is most likely to be colonized with resistant microbes acquired as a part of HAIs, which may endanger life. Source control should be done at the earliest by draining the collection.

Therapeutic Drug Monitoring (TDM): Especially for drugs like aminoglycosides, vancomycin, linezolid, teicoplanin, beta-lactams, quinolones, and antifungals, TDM is useful to improve infection clearance by maximizing efficacy and reducing toxicity. Usually, TDM for vancomycin should be > 5 mcg/mL, but the clinical practice guidelines recommend > 10 mg/mL to avoid drug resistance [30]. Steady state concentration of vancomycin 17–20 mg/L achieved by continuous infusion will achieve faster MRSA clearance. MIC (minimum inhibitory concentration) is the central component of the pharmacokinetics and pharmacodynamics of antimicrobials. MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation. Target trough aminoglycosides > 10 mg/L are more likely to improve clinical outcome [30].

Antibiotic Dosing in RRT: Factors affecting antibiotic levels in renal replacement therapy are volume of distribution (V), protein binding, molecular weight (MW), and clearance (CL). Extracorporeal fractional clearance is high for amikacin (95%), gentamicin (90%), fluconazole (87%), vancomycin (60%), and tazobactam (60%); moderate for ceftazidime (57%), colistin (51%), daptomycin (50%), levofloxacin (40%), meropenem (40%), and piperacillin (40%); and low clearance for teicoplanin (21%), linezolid (20%), ciprofloxacin (20%), and amphotericin B (12%). Repeat dosing should be given for drugs that have high or moderate clearance [31].

Fever in PICU

Fever is one of the most common yet difficult problems among critically ill children, and sometimes it is a physician's nightmare. The identification and treatment of fever in the ICU are very important as they directly influence mortality and morbidity [32]. According to the Infectious

Diseases Society of America (IDSA) and American College of Critical Care Medicine, jointly defined fever in the ICU as a temperature ≥ 38.3°C (101 F) [33]. A lower threshold is considered in immunocompromised patients as their febrile response is lower compared to that of normal individuals. Fever in neutropenic patients is defined as a single oral temperature of ≥ 38.3°C or oral temperature ≥ 38°C (100.4 F) sustained for > 1 h [33]. Hyperthermia is defined as a body temperature of ≥ 41°C, which is independent of the hypothalamic set point [34].

Temperature Measurement

There are various methods by which body temperature can be measured in ICU patients, the most common and pragmatic being the oral or axillary temperature measured by a digital thermometer. The gold standard method is intravascular thermistor at the pulmonary artery, which is seldom used [33].

Epidemiology

The incidence of fever in the pediatric ICU is about 50%, mostly due to hospital-acquired infections [32]. The prevalence varies depending on the spectrum of diseased patients handled and the strictness of asepsis and hand hygiene followed in the PICU. The new onset of fever worsens the existing condition as well as imposes new threats, thereby increasing mortality and prolonging the ICU stay.

Classification of Fever in ICU

Fever in the ICU can be broadly classified as infectious or noninfectious [34]; the most common being the infectious cause and that too health care infection.

Infectious Causes: Primary bloodstream infection, secondary bloodstream infection, ventilator-associated pneumonia, catheter-associated urinary tract infection, surgical site infection, sinusitis, and infected decubitus ulcer [33].

Noninfectious Causes: Drug fever, drug withdrawal, thrombophlebitis, venous thromboembolism, transfusion reactions, hemophagocytosis, autonomic instability, adrenal crisis, thyroid storm, neuroleptic malignant syndrome, and heat stroke [33]. In ICU patients, infectious causes are more commonly associated with septic shock than noninfectious causes.

Investigations

When a new onset fever is documented, one should ensure to examine the patient completely. Routine sepsis workup and necessary imaging should be performed. Simultaneously, noninfectious causes should also be screened if there are no clinical pointers to indicate a new infection. Clinical examination plays an important role in identifying the origin of fever and should not be underestimated. Hyperferritinemic sepsis is increasingly being identified nowadays and should be high on the cards, apart from routine hospital-acquired infections [35]. In extreme cases, invasive diagnostics like a biopsy can be done in search of a focus, and decision must be made on a case-to-case basis. Likewise, one should not miss the course and characteristics of baseline disease activity and its resistance to routine treatment. The complexity of the scenario will be handled smoothly only when the patient is regularly monitored and interpreted precisely.

Etiology

1) *Hospital-acquired infections:* HAIs are monitored and treated as discussed above.
2) *Postoperative fever:* Fever immediately in the postoperative period is a common finding due to the release of endogenous cytokines as an inflammatory response, but fever after 96 h or beyond the postoperative period is unlikely to be related to inflammation secondary to surgery [36].
3) *Central fever:* Injury to the hypothalamic thermoregulatory center will lead to a fever of unknown origin in a severely ill patient. Central fever starts earlier than infectious fever, continues longer, and is unresponsive to antibiotic treatment [37].
4) *Drug fever:* Drug fever involves many mechanisms such as hypersensitivity reactions, idiosyncratic reactions, altered thermoregulatory mechanisms, drug administration related, etc. and makes a clinician baffled in making a difference between drug-related fever and other conditions [38].
5) *Neuroleptic malignant syndrome & Malignant hyperthermia:* Point mutations in the *RYR1* receptor lead to sustained contraction of muscles, generating heat production that manifests as fever, rhabdomyolysis, electrolyte imbalance, etc. secondary to anesthetic or antipsychotic drug exposure [39].
6) *Thrombophlebitis:* When there is endothelial injury due to a massive cytokine storm induced by infection or any other etiology, the incidence of thrombophlebitis increases despite taking all preventive measures.

Removing the IV cannula will suffice in reducing fever [40].

7) *Unknown causes:* In rare circumstances where the etiology is unidentified, expert opinion and consensus should be taken on the management of fever after ruling out all possible etiologies.

Management

Based on the etiology, treatment for every fever varies. Hence, a thorough and targeted search should be carried out. Identification of origin, progression, intensity, correctable causes, infective and noninfective causes of fever are imperative. Empirical antibiotics are to be started at the suspicion of a new infection and followed up as per antibiotic stewardship.

Conclusion

HAIs are one of the most common causes of increased mortality and morbidity in the PICU. Device-related infections are most common; hence, one should follow strict asepsis and bundled care maintenance. Adherence to patient safety protocols, along with regular microbiological audits and antibiotic stewardship, will help tide over the situation. About 50% HAIs are preventable if asepsis and the judicious use of devices and lines are followed [3]. It is correct to say that "*ICU patients' outcome is in the hands of health care workers in ICU*," because hand hygiene is paramount above everything else and prevents the deadliest outcome.

Authors' Contributions AK: Abstract, personal protective measures, antibiotic stewardship, fever in PICU, conclusion; KP: Central line–associated BSI; RT: Catheter-associated UTI; MRS: Ventilator-associated pneumonia; AJ helped in conceptualization of the paper, manuscript writing, and critically reviewed the manuscript as submitted. AJ will act as the guarantor for this paper.

Declarations

Conflict of Interest None.

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