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Review Article

Perianal infections in acute leukemia patients who received induction and consolidation chemotherapy: Clinical manifestations, pathogenesis, complications, management, and prevention

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Abstract

Perianal infection (PI) is one of the complications often found in acute leukemia patients who received induction and consolidation chemotherapy. Perianal mucosal damage in these patients can be a port of entry of pathogenic microorganism. Clinical manifestations of PI can range from abscess and fistula to life-threatening complications of tissue necrosis and sepsis. Patients with neutropenia sometimes do not show profound signs of inflammation so that diagnosis sometimes requires imaging studies. These conditions not only cause death, but also decreases the patient's quality of life. Management of PI includes surgical and nonsurgical procedures, both of which show good results in most patients, however complications such as sepsis and necrosis can still be found. Prevention and early diagnosis of PI in leukemia patients are important and need to be developed.

***Keywords**: acute leukemia, chemotherapy, management, neutropenia, perianal infections*

Abstrak

Infeksi perianal (IP) merupakan salah satu komplikasi yang sering ditemukan pada pasien leukemia akut yang mendapatkan kemoterapi induksi dan konsolidasi. Pasien tersebut mengalami kerusakan mukosa perianal yang dapat menjadi *port de entrée* mikroorganisme patogen. Manifestasi klinis IP dapat berupa abses dan fistula hingga komplikasi nekrosis jaringan dan sepsis yang mengancam nyawa. Pasien dengan neutropenia terkadang tidak menunjukkan tanda inflamasi yang jelas sehingga penegakan diagnosis membutuhkan pemeriksaan penunjang dengan pencitraan. IP tidak hanya menyebabkan kematian, namun juga menurunkan kualitas hidup pasien. Tata laksana IP meliputi tindakan non-bedah dan bedah. Kedua tindakan tersebut menunjukkan hasil yang cukup baik pada sebagian besar pasien, namun komplikasi berupa nekrosis dan sepsis tetap dapat ditemukan. Untuk mengatasi hal tersebut perlu dikembangkan cara pencegahan dan diagnosis dini.

***Kata kunci**: infeksi perianal, kemoterapi, leukemia akut, tata laksana, pencegahan*

Background

Leukemia is a group of hematologic malignancy characterized by abnormal leukocyte proliferation and development. Until recently chemotherapy is one of the treatment options for leukemia. During induction-consolidation chemotherapy, neutropenia occurs and causes patients with leukemia become susceptible to infections.[1-3] One of the infections that frequently found is perianal infections (PI) which can manifest as abscess and fistula.[1,3] If it is not treated quickly, it will cause widespread infection and life-threatening sepsis.[3,4]

A study by Chen et al in Taiwan in 2013, which involved 1,102 adult patients with acute leukemia from 2001 to 2010 showed PI prevalence of 6.7% (74 patients). Twenty-three (31%) of 74 patients had recurrent PI.[2] A retrospective study from Turkey in 2016, with 79 acute leukemia patients who received chemotherapy, found that 34 patients had anorectal infection.[3] Other data from a study in Canada by Renzi et al In 2019, found 233 pediatric patients with acute myeloid leukemia (AML), 7% of the subjects experienced PI in the form of abscesses.[1] Based on data from Global Burden Cancer Study (GLOBOCAN) in 2020, the increase in the new number of leukemia cases in Indonesia was 14,979 cases with number of deaths of 11,530 cases.[5] However, there are no data that show the prevalence of PI either in adults or children.

Clinical Manifestation of Perianal Infections

The most common clinical manifestation of PI are abscess and fistula.[1,3,4,6] It is often accompanied by severe pain, swelling, and constipation.[2]

1. Abscess

An abscess is a localized collection of fluid. Perianal abscess occurs due to infection of cryptoglandular glands by bacteria. The inflammatory response begins with a neutrophil response, followed by the formation of pus which then formed an abscess. Abscess may form in submucosa, intermuscular, supralevator, and ischiorectal. The infection may resolve with an immune response or may become more severe, causing pain, swelling, and drainage.[4] In 2017, Chang et al. conducted a retrospective study of 292 patients data and found that in acute leukemia patients who received chemotherapy, the incidence of perianal abscess (PA) ranged from 5–9%. This study showed a low mortality rate of 14.3%, but it showed that patients with AP had a 10-fold risk experienced recurrent abscess after subsequent chemotherapy.[6,7]

2. Fistula

An abscess may heal permanently, but it may relapse in the same location and form drainage. This drainage or channel connects glands of cryptoglandular anal and perianal skin, this channel is called a perianal fistula (PF). It is estimated that one third of patients with PA may experience PF formation. PA is the acute manifestation of PI, and PF is the chronic manifestation.[2,4]

Pathogenesis

Leukemia is a group of blood malignancy disease characterized by the growth of immature progenitor cells in the bone marrow. Based on the degree of cell differentiation, leukemia can be classified into acute and chronic leukemia, while based on the dominant cell type involved, it can be divided into myeloid and lymphocytic. This disease may often cause thrombocytopenia, anemia and leukopenia. The exact cause of leukemia is unknown, non-specific symptoms include fever, fatigue, weight loss, bone pain, bruising, or bleeding. Acute leukemia can be divided into three types including, acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL) and the rare form which mixed form or mixed phenotype acute leukemia (MPAL).[9]

Patients with leukemia are susceptible to infection. Infection is caused by complex interaction between disease, immune system, and pathogenic bacteria, causing significant morbidity and mortality. The severity of infection is influenced by several factors, the disease-related factors, patient-related factors and treatment-related factors.[9] (Figure 1)

Leukemia treatment, particularly chemotherapy is divided into induction phase, consolidation phase and maintenance phase. Induction phase chemotherapy is the first chemotherapy that aims to destroy leukemia cells in the bone marrow. Consolidation phase is a follow-up treatment to remove residual leukemia cells after induction phase, while maintenance phase is provided to prevent recurrence and maintain long-term remission.

1. Disease-related factors

In patients with leukemia, the normal function of bone marrow become disrupted so that proliferative cells experience abnormal maturation (immature) and

result in the interference of granulocyte function and decrease in the number of immune cells in the blood circulation. It makes the organism more susceptible to infection. Furthermore, abnormal cells have the potential to inhibit response of antigen specific T-cells, in addition there is a decrease in the humoral immune system, therefore most patients will experience immunoglobulin deficiency.[9] In AML there is a unique immune dysregulation which can avoid the body's immune system by controlling and actively suppresses the immune response (immune editing and immune evasion).[10] Certain chemotherapy regiments at induction phase in AML also causes neutropenia that last longer than the induction phase in ALL, so that the incidence and the severity of infection in AML patients is higher than in ALL patients.[9,10]

2. Patient-related factors

a. Age

Patient's age is important in assessing the risk of infection in acute leukemia patients. The natural function of the immune system declines with increasing age, such as the function of B and T cells. In elderly people the condition of imbalance between inflammatory and anti-inflammatory mechanisms leads to remodeling and the up regulation of pro-inflammatory cytokines. This condition known as immunosenescence and caused a modification of apoptotic lymphocytes.[10] Elderly patients also often have comorbidities that affect the choice and dose of treatment, thereby increase the risk of disease morbidity and mortality.[11]

b. Nutrition

Nutrition is also considered as one of the factors that influence infection susceptibility. Nutritional problems are often associated with side effects of leukemia treatment, such as nausea and vomiting. Reduced food intake, low baseline body mass index (BMI) and weight loss during treatment are strong indicators of low survival rates and bacterial and fungal infection.[15]

3. Treatment-related factors

Leukemia treatment requires intensive chemotherapy with certain drug doses and might last for certain period of time so that result in prolonged neutropenia. The risk of infection is influenced by the degree and duration of the neutropenia. Gill et al found cytopenia in patient with chronic lymphocytic leukemia (CLL) namely the decrease in the number of mature blood cells, which lasts more than 3 months after combination chemotherapy with fludarabine.[16] This condition is associated with susceptibility to infection including prolonged neutropenia. A study by Solmaz showed that leukemia patients in the neutropenic period were more susceptible to anorectal infections that manifest as abscess or fistula.[3]

Leukemia patients who receive chemotherapy will experience mucosal barrier injury, or often called mucositis.[17.18] Under normal circumstances mucosa will protect the body against pathogenic micro-organisms and at the same time it provides defense against normal microorganisms (resident micro-organisms). Damage on the mucosa of gastro-intestinal tract could be a place for microorganisms to enter (*port de entrée*) and potentially causing infection. As a result, infection in leukemia patients is frequently caused by normal microorganisms that inhabit the skin, oral cavity, and gastrointestinal tract, such as, *E. coli, Klebsiella spp.* and *Viridans group streptococci.* These organisms under normal circumstances can be found in large numbers but it does not cause any infection symptoms.[19]

Leukemia treatment also affects the colonization of bacteria or the normal flora of the gastrointestinal tract (GIT) which we call the commensal microbiota. Furthermore, the decrease in the number of the normal flora will reduce microbial diversity which plays a role in suppressing infection.[19] The change in GIT microbiota happened through indirect and direct mechanism (Figure 1)

Indirect mechanisms (Fig. 2 A–C) involve the gut microbiota in defense against pathogenic bacteria through direct and indirect mechanisms of action. Commensal bacterial species and their products interact with the host by producing antimicrobial peptides, maintaining the epithelial barrier, and modulating bile acids. Antimicrobial proteins are REG3 gamma protein and angiogenin-4 (ANG4). The proinflammatory cytokine IL-18 increases the production of antimicrobial peptides, including ANG4. Certain commensal bacteria, such as *Clostridium scindens*, can cause hydroxylation of primary bile acids to secondary bile acids using the 7α-hydroxysteroid dehydrogenase enzyme, which inhibits the growth of *C. difficile*. The microbiota also maintains the epithelial barrier by producing mucus, and transcription activation of nuclear factor-κB (NF-κB) in epithelial cells to delay apoptosis and repair tissue.

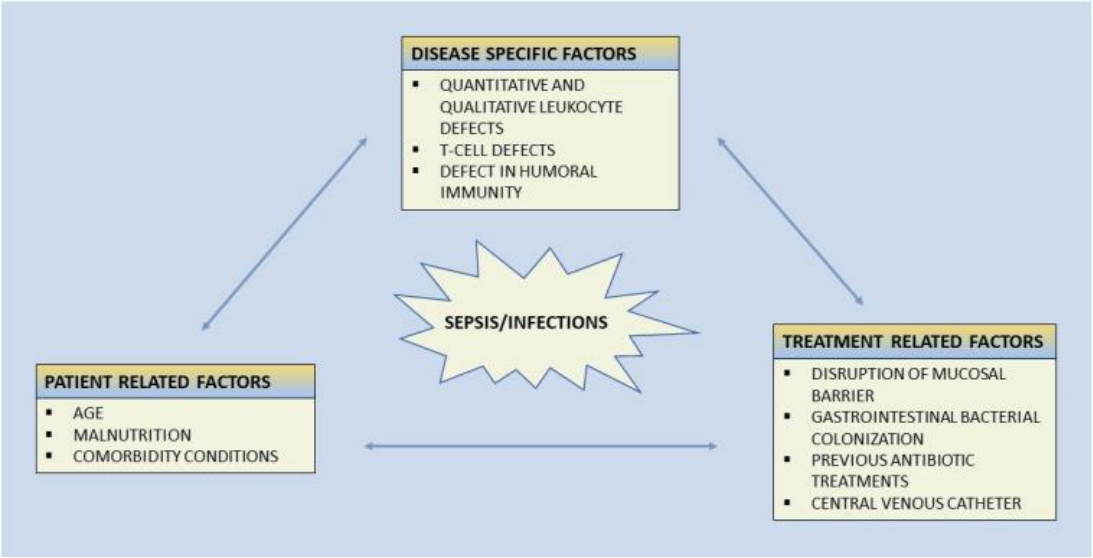

Figure 1. Interactions of factors that influences the pathogenesis of PI in leukemia patients. Quoted with modification from reference no. 9

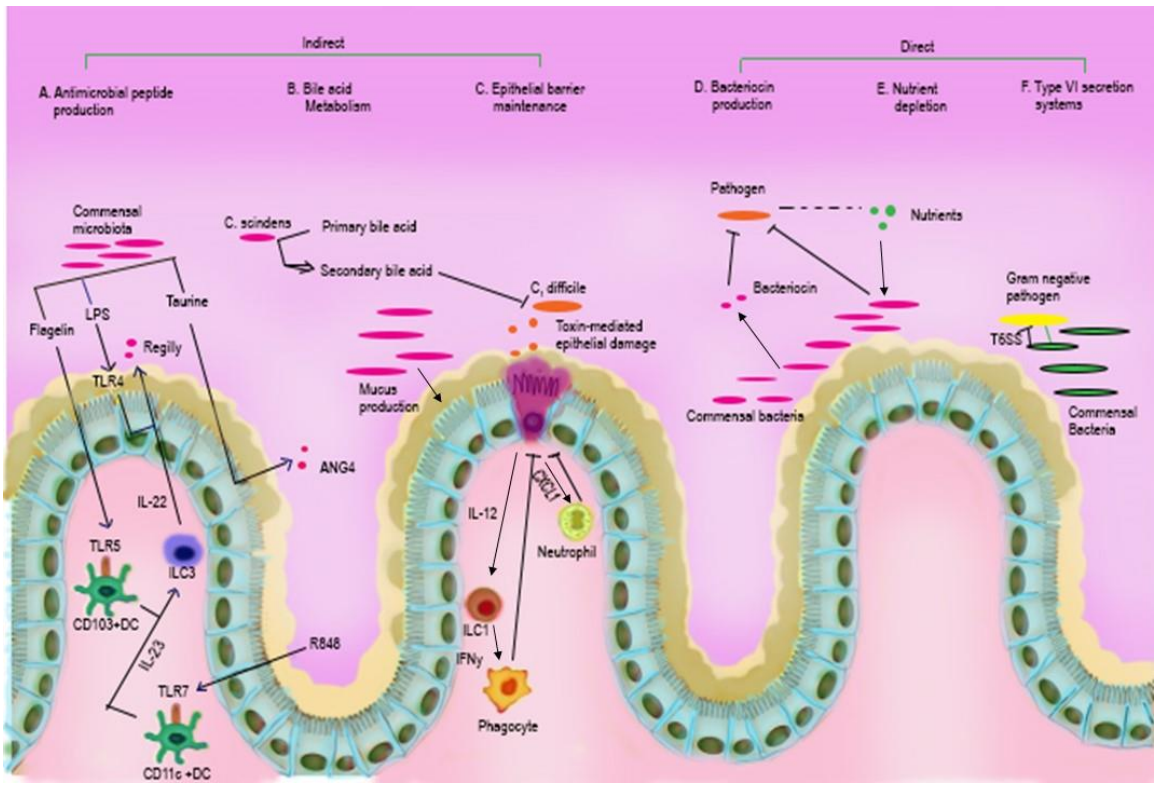

Figure 2. **A-C:** Indirect mechanisms, **D-F**: Direct mechanisms. Quoted with modification from references no. 2

Direct mechanisms of colonization resistance include bacteriocin production, nutrient depletion, and the type VI secretion system (Fig. 2 D-F). Several commensal bacterias have been identified to produce bacteriocins with a narrow spectrum of activity, which inhibit specific pathogens with minimal impact against other commensal microbiota (Fig. 2 D). In addition, commensal microbiota will compete with pathogens in receiving various nutrients, including food and carbohydrates that are obtained from the host, as well as producing metabolites such as succinate, that decrease pathogens colonization (Fig.2 E).[17-19]

The use of broad-spectrum antibiotics, particularly beta-lactams and cephalosporins, is a routine practice to prevent opportunistic infection in patients. However, there are consequences of inappropriate antibiotics use. Its administration will affect the number of gastrointestinal tract microbiota, so that the colonization of certain bacteria such as *Clostridium difficile* will increase and cause infection. Other nosocomial pathogens bacteria can also grow and enter the bloodstream, causing systemic infections. Table 1 contains the names of common GIT bacterias that frequently cause infections.[19,20]

A study by Chen et al reported that perianal infections were most often caused by bacteria (99%) and Candida species (1%). Overall, 68% of patients had polymicrobial infection, and 24% had bacteremia. The most frequently isolated bacteria in this study were *Escherichia coli* (25%), followed by *Enterococcus* species (22%), *Klebsiella pneumonia* (13%), and *Bacteroides* species (11%).[17]

In addition to the microorganisms mentioned above, infection can also be caused by other skin commensal bacteria, one of which is *S. epidermidis*. These bacteria not only cause skin infection around the perianal, but infection can also be caused by medical action such as the installation of a central venous catheter (CVC).[9]

Table 1. Common gastrointestinal bacteria that cause infections in leukemia patients

	Microorganisms	**Source**
Gram-negative bacteria	*E. faecalis* *E. faecium*	Gastrointestinal tract[19,24]
	C. difficile	Lower gastrointestinal tract[19,25]
	Viridans group streptococci	Oral/ Gastrointestinal tract[19,26-29]
Gram-negative bacteria	*E. coli*	Gastrointestinal tract, urogenital [19,24,30-35]
	Klebsiella spp	Gastrointestinal tract, urogenital [19,24,30-35]
	P. aeruginosa	Gastrointestinal tract[19,24,36,37]

Diagnosis

History and physical examination

Signs of infection include fever (temperature >38°C), complaints of perianal pain. In physical examination, it was found perianal mass, induration, erythema, fluctuation, and purulent fluid was found when ruptured. These signs may not appear simultaneously. Neutropenia in patients may cause an inflammatory response that is different with immunocompetent patients so that the symptoms of perianal erythema and induration may be less prominent.[1,2,21]

Diagnostic examination

- Blood culture

Cultures (blood, fluid) will help identifying cause of infection. Blood culture should ideally be taken during fever and before antimicrobial administration. The discovery of microbes and their sensitivity to antimicrobials becomes important for patients' treatment.

- Imaging examination

If clinical signs are not characteristic, imaging studies can be performed. Magnetic Resonance Imaging (MRI) with contrast administration supporting investigation, produces optimal imaging of the soft tissues.[1,2,22,23] A study by Plumb et al (2015) found high signal intensity in patients with PA, which was significantly greater in patients with hematological malignancies compared to patients' control. MRI can also show the location of the fistula and then facilitate surgery.[23]

Supporting investigation with computed tomography scan (CT scan) is also useful in diagnosing PA. Large PA will be seen on CT scan, however if the size of the

PA and fistula is small, there is a possibility that the abnormality is not visible. Moreover, soft tissue resolution with CT scan is not as good as MRI examination.[23]

Another examination that also helpful is imaging with ultrasonography (USG). A study by Cheng et al showed that imaging with USG itself is quite helpful. This procedure is inexpensive and has a low radiation risk. But still it has some limitations in detecting small PA and PF, and since sound doesn't penetrate well through bone, USG is not effective at imaging PA and PF that are hidden by bones. In addition, patients with severe pain or pediatric patients may require sedation.

Complications

Blood Stream Infection

Blood stream infection (BSI) that originates from the gastrointestinal tract can occur in patients with compromised immune systems. The combination of chemotherapy, antibiotics and dysregulation of the immune system in leukemia patients results in impaired immune system and gastrointestinal mucositis. Pathogenic microorganisms enter through *port de entrée* in gastrointestinal tract and spread systemically.[2,9,19]

Sepsis

Sepsis is a life-threatening condition, caused by response of the body to infection, which is characterized by organ failure.[38] Finding signs of sepsis in leukemia patients is challenging because leukemia causes altered inflammatory response. However, sepsis should still be suspected in patients with either fever symptoms (>38°C) or hypothermia (<36°C), heart rate (>90 per minute), tachypnea (>30 breaths per minute), altered mental status, signs of significant edema or positive fluid balance (>20 ml/ kg over 24 hours), and hyperglycemia (plasma glucose >110 mg / dl or 7,7 mmol / l) in patients without a history of diabetes. In addition, it is necessary to pay attention to symptoms of infection such as respiratory symptoms (cough, rhinorrhea, and respiratory disorders), digestive symptoms (nausea, vomiting, diarrhea, and stomachache), and impaired consciousness.

Hemodynamic parameters can indicate organ dysfunction and sepsis development; hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70 mmHg, or decreased systolic blood pressure >40 mmHg in adults or <2 standard deviations (SD) below normal for age, mixed venous oxygen saturation >70%, heart index (cardiac index >3,5 l / min / m^2, arterial hypoxemia (PaO2 / FiO2 <300), and acute oliguria (urine output <0,5 ml / kg / hour or 45 ml for at least 2 hours).[39, 40]

Laboratory testing helps estimate the severity of the infection and may show the source of the infection. Inflammatory markers that show sepsis are leukocytosis (white cell counts (WBC)> 12 x 10^9/l), leukopenia (WBC <4 x 10^9/l), normal white blood cell count with >10% immature form, and C-reactive protein (CRP) or procalcitonin >2 Standard Deviation. Organ dysfunction can also be verified by laboratory testing including creatinine increase ≥0,5 mg / dl, coagulation abnormalities (International Normalized Ratio (INR) >1,5 or activated partial thromboplastin time (APTT) >60 seconds), thrombocytopenia (platelets <100 000 / µl), and hyperbilirubinemia (plasma bilirubin total >4 mg / dl or 70 µmol / l). Hyperlactatemia (>3 mmol / l) may indicate decreased tissue perfusion.[39,40]

Fournier gangrene

Fournier gangrene (FG) is a necrotizing fasciitis that occurs in the genital area, perineum, anus, and sometimes in the skin of the lower abdomen. Immune deficiency is one of the risk factors for FG. In PI, there is skin discontinuity, therefore it can become *port de entrée* for variety of pathogenic microorganisms. Both conditions allow the occurrence of FG in leukemia patients who received chemotherapy and experienced PI.[41]

A case report by Mantadakis et al, showed that FG may occur in young adult patients who were receiving induction phase chemotherapy. In 2016, Solmaz et al investigated perianal complication that occurred in 92 acute leukemia patients who were undergoing induction-consolidation phase chemotherapy. The study showed that 19 patients who had PA, 1 patient had necrosis on perianal area or FG.[3,42] Another study by Renzi et al, with research subjects of 235 pediatric patients, showed that 7% of the subjects or 19 patients had perianal infections, and there were two patients with PA which progressed into FG.

Management

Management of PI in leukemia patients differs from immunocompetent patients. This is due to immunosuppression and pancytopenia conditions that occur during chemotherapy. It is important to conduct multidisciplinary management that involves collaboration

between oncologists, surgeons, and infectious disease experts.

Management includes surgical treatment (ST) and non-surgical treatment (NST). The criteria for selecting the two managements are still unclear. Studies of the two management options showed varied results. Some studies suggest that ST should be performed immediately in leukemia patients with PI, but other studies showed that NST alone is sufficient.[7,43]

- Surgical treatment (ST)

The ST approach in leukemia patients should consider neutropenia and thrombocytopenia conditions. ST is performed very selectively for patients with obvious clinical manifestations of abscess. Patients who do not show improvement with the NST approach itself may be considered for receiving ST.[7,43]

A study by Barnes et al suggested early surgical intervention and abscess drainage. The study involved 16 patients with perianal abscess. Fifteen of 16 leukemia patients experienced improvement. The authors suggested that drainage was an important procedure that would eliminate source of infections and induce neutrophil recovery.[43]

A more recent study by Badgwell et al attempted to determine factors or predictors for PI management. This study is a retrospective study which involved 100 patients with neutropenia (Absolute Neutrophil Count < 1000 cells/ml), the study found that abscess and signs of erythema are indications of ST.[44] Both studies suggested that ST should be conducted on patients that had a prominent abscess on clinical manifestations nor supporting investigations, significant necrosis, and soft tissue infection despite appropriate antibiotics administration. ST selection should still consider the condition of neutropenia and the patient's bleeding risk.

- Non-surgical treatment (NST)

The NST approach relies on antimicrobials. Once a potential source of infection is identified, either from laboratory tests or blood cultures, the patient should begin antimicrobial therapy immediately. The recommended antibiotics should have broad spectrum activity gram-positive, gram-negative, anaerobic bacteria, and antifungals. Administration of broad-spectrum antibiotics is important because in patients with leukemia, polymicrobial pathogens are common.[2,19,24-37]

Patients without signs of erythema, abscess, and perianal fluid on physical examination, but showed the presence of PI features from supporting investigation of MRI and CT scan can be considered for NST management. This treatment can be used as an alternative option, considering the presence of neutropenia, thrombocytopenia, poor vital signs and poor laboratory results. However, this approach requires close monitoring to avoid complications such as BSI and sepsis.

The knowledge of microbiological patterns and microbial resistance in hospital is important for the selection of antimicrobial therapy. When a particular pathogen is identified from laboratory and culture results, the selection of antimicrobial should be based on these results and clinical manifestations.

A study by Lehrnbecher et al of National Cancer Institute (NCI), USA, examined 82 episodes of PI in 64 leukemia patients after induction chemotherapy. The study showed antibiotics therapy alone was successful in PI treatment of 52/82 (63%) episodes. The combination of ST and NST was needed in 25/82 (31%) episodes, and only 5 patients needed ST management alone.[47]

Table 2. The use of antibiotics based on European Conference on Infections in Leukemia guidelines (ECIL) and Infectious Disease Society of America (IDSA)

Microbes		Recommended antibiotic treatment options
Gram-negative bacteria	ESBL	Carbapenems
	CPE	Two or more combinations, aminoglycosides, polymyxins, tigecycline, fosfomycin, and meropenem
	P. aeruginosa	Combination therapy, using a beta-lactam with an aminoglycoside or a fluoroquinolone
	S. maltophilia	Trimethoprim-sulfamethoxazole (combination with ticarcillin/clavulanate or ceftazidime)
	MDRO *A.baumanii*	Colistin Combination with ampicillin/sulbactam or imipenem or meropenem. Tigecycline Combination
Gram-positive bacteria	CoNS	Glycopeptides; vancomycin and teicoplanin (daptomycin, linezolid, and tigecycline)
	MRSA	
	VRE	Linezolid and daptomycin (Quinupristin–dalfopristin, tigecycline, fosfomycin, tedizolid, oritavancin, dalbavancin and telavancin)

ESBL: *Broad-Spectrum β-Lactamase-Producing Enterobacteriaceae*. CPE: *Carbapenemase-Producing Enterobacteriaceae*. MRSA: *Methicillin-resistant Staphylococcus aureus*. CoNS: *Coagulase-negative Staphylococcus*. VRE: *Vancomycin Resistant Enterococci*. MDRO: *Multidrug-resistant Organism.*
Quoted with modification from references no. 9, 24, 26-37.

Table 3. The use of antifungals based on European Conference on Infections in Leukaemia guidelines (ECIL) and Infectious Disease Society of America (IDSA)

Microbes		Recommended antifungal treatment options
Fungal infection	*P. jiroveci*	Trimetoprim-sulfamethoxazole (Primaquine + clindamycin, pentamidine)
	Candida spp.	Echinocandins (Fluconazole)
	Aspergillus spp.	Voriconazole, isavuconazole (Liposomal, amphotericin B, caspofungin)

Drugs in parentheses are second-line alternatives
Quoted with modification from references of no. 9, 45, 46.

- Sitz bath

Sitz bath (SB) is a therapeutic method of warm water added with certain drugs or substances to clean area around perineum and genitals. Patients can soak the perineum area with the solution. In post-chemotherapy leukemia patients with signs of PI, SB can be performed to treat and prevent worsening of PI. Substances that are added to warm water are generally potassium permanganate (PP) with a concentration of 1:5000.[48.49]

In 2020, Zhou et al conducted a retrospective study of SB effectiveness using matrine compounds (matrine sitz bath/MSB) compared to PP. This study involved 216 leukemia patients with PI. The results showed that perianal pain, systemic symptoms, PA size and consistency improved in both treatment groups. However, the group with MSB therapy showed a more significant improvement compared to the PP group (control) ($p < 0,05$). Analysis was also conducted by examining blood inflammatory markers, namely level of proinflammatory factor of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor (TNF-α), erythrocyte sedimentation rate (ESR) and prostaglandins E2 (PEG2). All of these blood inflammatory markers decreased in both the MSB and PP groups, so it was concluded that the SB method could reduce inflammation.[48]

Prevention

PI is common in leukemia patients after chemo-therapy, and it caused significant morbidity and mortality.[2,3,6] On the other hand, the management of ST and NST shows varied results. Therefore, it is

necessary to think about PI prevention strategies in leukemia patients.

A study in China has compiled a concept of prevention which involves doctors, nurses, laboratory technicians and residents. This concept is called a quality control circle (QCC) or can also be called a plan-do-check-act (PDCA). The steps contained in the QCC including, planning, analysis of causes, implementation, and standardization. With the QCC concept, PI prevention is performed by teaching patients to recognize PI signs as early as possible.[49]

The followings are the steps in QCC or PDCA:

1. Planning

The QCC team members consist of 5-9 doctors, analysts, nurses and medical students. The QCC team will provide questionnaires to patients to recognize several factors that can influence the severity of PI. Some of these factors will become the basis for the management or actions that are arranged in the PDCA.

2. Cause analysis

The causes or factors that have been obtained by giving questionnaires will be the focus of the QCC team's intervention. In a study by Jiang et al at Nanfang Hospital, China, the factors that cause the high incidence of PI including the lack of patient knowledge about PI, lack of standard operating procedures (SOP) for skin disinfection, and lack of disinfection tools and materials. The QCC team then uses the "5W1H" principles (who, what, when, where, why, and how) to compile actions to intervene these issues.

3. Implementation

At this phase the QCC team conducts the interventions that have been compiled. To overcome the patient's lack of knowledge about PI, doctors, nurses, and medical students educate patients to recognize and treat PI signs and provide tools and materials for PI treatments. The QCC team also educates the patient's family. The education is performed in group discussions, giving notes or brochures of proper PI treatments.

4. Standardization

PI prevention efforts are assessed and reviewed every 9 months. If there is a procedure that does not give benefits, then the procedure is eliminated. On the contrary, procedures that are assessed to be able to reduce the severity of PI are maintained. Then the procedure is used as a standard of treatment and documented in the form of videos or recordings that are shared with other patients.

The objective of QCC is to reduce the incidence of PI which will also reduce mortality, length of hospital stays, and cost of treatment. This QCC study involved 253 patients with hematological malignancies and was conducted for one year. After one year of follow-up, it was obtained that PI incidence rate decreased from 17.20% to 5.93% and remained at 5.25% during the following year.[49]

Conclusion

PI is a complication that is common in acute leukemia patients who receive induction and consolidation chemotherapy. The pathogenesis of PI involves the interaction of many factors, namely, disease, patients, and treatment factors. Early diagnosis is challenging and requires supporting examinations. Management of PI consist of NST and ST procedures, both showed varied results. It is necessary to think of preventive measures on PI to reduce the incidence rate, morbidity, length, and cost of treatment in hospital. QCC methods can be used as a guide for the prevention of PI in leukemia patients who receive induction and consolidation chemotherapy.

Conflict of Interests

There is no conflict of interests that need to be declare.

References

1. Renzi S, Bartram J, Ali S, Portwine C, Mitchell D, Dix D, et al. Perianal Infections in Children with Acute Myeloid Leukemia: A Report from the Canadian Infection in Acute Myeloid Leukemia Research Group. J Pediatric Infect Dis Soc. 2019;8(4):354-7.
2. Chen CY, Cheng A, Huang SY, Sheng WH, Liu JH, Ko BS, et al. Clinical and microbiological characteristics of perianal infections in adult patients with acute leukemia. PLoS One. 2013;8(4):e60624.
3. Solmaz S, Korur A, Gereklioglu C, Asma S, Buyukkurt N, Kasar M, et al. Anorectal Complications During Neutropenic Period in Patients with Hematologic Diseases. Mediterr J Hematol Infect Dis. 2016;8(1):e2016019.
4. Sahnan K, Adegbola SO, Tozer PJ, Watfah J, PhillPI s RK. Perianal abscess. BMJ. 2017;356:j475.

5. International agency for research on cancer. https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf 2020.
6. Chang H, Kuo MC, Tang TC, Lin TL, Wu JH, Hung YS, et al. Clinical Features and Recurrence Pattern of Perianal Abscess in Patients with Acute Myeloid Leukemia. Acta Haematol. 2017;138(1):10-3.
7. Amato A, Bottini C, De Nardi P, Giamundo P, Lauretta A, Realis Luc A, et al. Evaluation and management of perianal abscess and anal fistula: SICCR position statement. Tech Coloproctol. 2020;24(2):127-43.
8. Lyengar V, Shimanovsky A. Leukemia. Treasure Island (FL): StatPearls Publishing. 2020;PMID: 32809325.
9. Hansen BA, Wendelbo O, Bruserud O, Hemsing AL, Mosevoll KA, Reikvam H. Febrile Neutropenia in Acute Leukemia. Epidemiology, Etiology, Pathophysiology and Treatment. Mediterr J Hematol Infect Dis. 2020;12(1):e2020009.
10. Ventura MT, Casciaro M, Gangemi S, Buquicchio R. Immunosenescence in aging: between immune cells depletion and cytokines up-regulation. *Clin Mol Allergy*. 2017;15:21.
11. Barrett AJ. Acute myeloid leukaemia and the immune system: implications for immunotherapy. Br J Haematol. 2020;188(1):147-58.
12. Atkins S, He F. Chemotherapy and Beyond: Infections in the Era of Old and New Treatments for Hematologic Malignancies. Infect Dis Clin North Am. 2019;33(2):289-309.
13. Kayser S, Levis MJ. Advances in targeted therapy for acute myeloid leukaemia. Br J Haematol. 2018;180(4):484-500.
14. Halpern AB, Culakova E, Walter RB, Lyman GH. Association of Risk Factors, Mortality, and Care Costs of Adults with Acute Myeloid Leukemia With Admission to the Intensive Care Unit. JAMA Oncol. 2017;3(3):374-81.
15. Baumgartner A, Zueger N, Bargetzi A, Medinger M, Passweg JR, Stanga Z, et al. Association of Nutritional Parameters with Clinical Outcomes in Patients with Acute Myeloid Leukemia Undergoing Haematopoietic Stem Cell Transplantation. Annals of Nutrition and Metabolism. 2016;69(2):89-98.
16. Gill S, Carney D, Ritchie D, Wolf M, Westerman D, Prince HM, et al. The frequency, manifestations, and duration of prolonged cytopenias after first line fludarabine combination chemotherapy. Ann Oncol. 2010;21(2):331-4.
17. France MM, Turner JR. The mucosal barrier at a glance. J Cell Sci. 2017;130(2):307-14.
18. Van der Velden WJ, Herbers AH, Netea MG, Blijlevens NM. Mucosal barrier injury, fever, and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. Br J Haematol. 2014;167(4):441-52.
19. Kim S, Covington A, Pamer EG. The intestinal microbiota: Antibiotics, colonization resistance, and enteric pathogens. Immunol Rev. 2017;279(1):90-105.
20. Luo R, Greenberg A, Stone CD. Outcomes of Clostridium difficile infection in hospitalized leukemia patients: a nationwide analysis. Infect Control Hosp Epidemiol. 2015;36(7):794-801.
21. Iqbal S, Walcott J, Chan S. Acute Myelomonocytic Leukemia Presenting as Perianal Pain. Case Rep Surg. 2018:2151492.
22. Haliloglu N, Gulpinar B, Ozkavukcu E, Erden A. Typical MR imaging findings of perianal infections in patients with hematologic malignancies. Eur J Radiol. 2017;93:284-8.
23. Tolan DJ. Magnetic Resonance Imaging for Perianal Fistula. Semin Ultrasound CT MR. 2016;37(4):313-22.
24. Satlin MJ, Walsh TJ. Multidrug-resistant Enterobacteriaceae, Pseudomonas aeruginosa, and vancomycin-resistant Enterococcus: Three major threats to hematopoietic stem cell transplant recPI ients. Transpl Infect Dis. 2017;19(6).
25. Bartlett JG: Narrative review: the new epidemic of Clostridium difficileassociated enteric disease. Annals of internal medicine 2006, 145(10):758-64.
26. Torfoss D. Carbapenems and febrile neutropenia - author's reply. Clin Microbiol Infect. 2017;23(3):214.
27. Torfoss D, Fladhagen T, Holte H, Brinch L, Schjesvold FH, Floisand Y, et al. Benzylpenicillin plus an aminoglycoside versus meropenem in neutropenic lymphoma and leukaemia patients with a suspected bacterial infection: a randomized, controlled trial. Clin Microbiol Infect. 2017;23(3):179-87.
28. Torfoss D, Hoiby EA, Holte H, Kvaloy S. The Norwegian experience with penicillin G plus an aminoglycoside as initial empiric therapy in febrile neutropenia; a review. Acta Oncol. 2012;51(4):433-40.
29. Torfoss D, Hoiby EA, Tangen JM, Holte H, Bo K, Meyer P, et al. Tobramycin once versus three times daily, given with penicillin G, to febrile neutropenic cancer patients in Norway: a prospective, randomized, multicentre trial. J Antimicrob Chemother. 2007;59(4):711-7.
30. Perez F, Adachi J, Bonomo RA. Antibiotic-resistant gram-negative bacterial infections in patients with cancer. Clin Infect Dis. 2014;59 Suppl 5:S335-9.
31. Gudiol C, Royo-Cebrecos C, Tebe C, Abdala E, Akova M, Alvarez R, et al. Clinical efficacy of beta-lactam/beta-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in haematological patients with neutropaenia: a study protocol for a retrospective observational study (BICAR). BMJ Open. 2017;7(1):e013268.
32. Bassetti M, Giacobbe DR, Giamarellou H, Viscoli C, Daikos GL, Dimopoulos G, et al. Management of KPC-producing Klebsiella pneumoniae infections. Clin Microbiol Infect. 2018;24(2):133-44.
33. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh P-R, Viale P, Paño-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. The Lancet Infectious Diseases. 2017;17(7):726-34.
34. Gutierrez-Gutierrez B, Perez-Galera S, Salamanca E, de Cueto M, Calbo E, Almirante B, et al. A Multinational, Preregistered Cohort Study of beta-

Lactam/beta-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-beta-Lactamase-Producing Enterobacteriaceae. Antimicrob Agents Chemother. 2016;60(7):4159-69.
35. Averbuch D, Cordonnier C, Livermore DM, Mikulska M, Orasch C, Viscoli C, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recPI ients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica. 2013;98(12):1836-47.
36. Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, Pabst T, Ozcelik T, Klyasova G, Donnini I et al: Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant RecPI ients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. Clin Infect Dis 2017, 65(11):1819-1828
37. Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect. 2018;76(1):20-37.
38. Huerta LE, Rice TW. Pathologic Difference between Sepsis and Bloodstream Infections. J Appl Lab Med. 2019;3(4):654-63.
39. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29(4):530-8.
40. Kim M, Ahn S, Kim WY, Sohn CH, Seo DW, Lee YS, et al. Predictive performance of the quick Sequential Organ Failure Assessment score as a screening tool for sepsis, mortality, and intensive care unit admission in patients with febrile neutropenia. Support Care Cancer. 2017;25(5):1557-62.
41. LaChance A & Kroshinksy D. Necrotizing Fasciitis, Necrotizing Cellulitis, and Myonecrosis. In: Kang S, Amagai M, Bruckner AL, Enk AH, Morgolis DJ, McMichael AJ, et al, editors. Fitzpatrick's Dermatology 9th Ed: McGraw-Hill Education. 2019;2770-81
42. Mantadakis E, Pontikoglou C, Papadaki HA, Aggelidakis G, Samonis G. Fatal Fournier's gangrene in a young adult with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2007;49(6):862-4.
43. Baker B, Al-Salman M, Daoud F. Management of acute perianal sepsis in neutropenic patients with hematological malignancy. Tech Coloproctol. 2014;18(4):327-33.
44. Badgwell BD, Chang GJ, Rodriguez-Bigas MA, Smith K, Lupo PJ, Frankowski RF, et al. Management and outcomes of anorectal infection in the cancer patient. Ann Surg Oncol. 2009;16(10):2752-8.
45. Maschmeyer G, Helweg-Larsen J, Pagano L, Robin C, Cordonnier C, Schellongowski P, et al. ECIL guidelines for treatment of Pneumocystis jirovecii pneumonia in non-HIV-infected haematology patients. J Antimicrob Chemother. 2016;71(9):2405-13.
46. Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102(3):433-44.
47. Lehrnbecher T, Marshall D, Gao C, Chanock SJ. A second look at anorectal infections in cancer patients in a large cancer institute: the success of early intervention with antibiotics and surgery. Infection. 2002;30(5):272-6.
48. Zhou Y, Gao H, Hua H, Zhu W, Wang Z, Zhang Y, et al. Clinical effectiveness of matrine sitz bath in treating perianal infection after chemotherapy for acute leukemia. Ann Palliat Med. 2020;9(3):1109-16.
49. Jiang Q, Zhang D, Majaw J, Zhao C, Chai Y, Xu Z, et al. Minimization of the perianal infection rate of hematological malignancies with agranulocytosis by quality control circle activity and patient-hospital-student win-win concept. J Int Med Res. 2018;46(6):2338-45.