Preventing transmission of infectious agents in the pediatric in-patients hematology-oncology setting: what is the role for non-pharmacological prophylaxis?

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Abstract

The most intensive chemotherapy regimens were used in the past for leukemia patients who were the main focus of trials on infections; today there are increasing numbers of children with solid cancer and considerable risk of infection who do receive intensive standard-dose chemotherapy. Despite a continuous will to protect the immune-compromised child from infections, evidence-based indications for intervention by non-pharmacological tools is still lacking in the pediatric hematology-oncology literature. Guidelines on standard precautions as well as precautions to avoid transmission of specific infectious agents are available. As a result of a consensus discussion, the Italian Association for Pediatric Hematology-Oncology (AIEOP) Cooperative Group centers agree that for children treated with chemotherapy both of these approaches should be implemented and vigorously enforced, while additional policies, including strict environmental isolation, should be restricted to patients with selected clinical conditions or complications. We present here a study by the working group on infectious diseases of AIEOP.

Introduction

In the past the most intensive chemotherapy regimens were used for leukemia patients who were the main subjects for trials on infections, and today there is an increasing number of children with solid cancer who are at considerable risk for infection and who receive intensive standard-dose chemotherapy.[1]

The aim of non-pharmacological prophylaxis is to reduce the risk of transmission of infection to the patient as much as possible while he/she is in the ward. This has been the object of specific guidelines by the Centers for Disease Control (CDC), published in 2007.[2] However, these guidelines are general recommendations for any hospital environment and not specific for the immunocompromised host, particularly the pediatric oncology patient. Furthermore, most recommendations are based on uncontrolled studies or experts' opinions rather than on randomized controlled trials, and they frequently refer to patients undergoing hematopoietic stem cell transplantation (HSCT), while no specific recommendations are available for patients treated with chemotherapy alone.[3]

In an attempt to provide uniform criteria in this field, the Italian Association for Pediatric Hematology-Oncology (AIEOP) organized a consensus conference at which the issue was debated. We present a paper by the working group on infectious diseases of AIEOP, which includes suggestions of standard precautions for any patient (Table 1), and of solutions to prevent specific transmission-based infections (Table 2).[2]

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Background knowledge

Several host factors can increase susceptibility to infection, including the following: a variety of medications that alter the normal flora (e.g. antimicrobial agents, gastric acid suppressants, corticosteroids, immune suppressive drugs, antineoplastic agents, and immunosuppressive drugs); surgical procedures and radiation therapy that impair defenses of the skin and other involved organ systems; indwelling devices such as central venous (or arterial) catheters, which facilitate development of infections by allowing potential pathogens to bypass local defenses. This would ordinarily impede their invasion, and provide surfaces for development of bio-films that may facilitate adherence of microorganisms and protect from antimicrobial activity.[4-6] Children with cancer may have additional risk factors owing to their age and age-related behaviors: an increased numbers of close physical contacts between them and healthcare personnel may occur because of cuddling, feeding, playing, changing soiled diapers, and cleaning copious uncontrolled respiratory secretions. This may provide abundant opportunities for transmission of infectious material. Practices and behaviors such as congregation of children in play areas where toys and body secretions are easily shared, and family members rooming in can further increase the risk of transmission. Pathogenic bacteria have been recovered from toys used by hospitalized patients; contaminated bath toys were implicated in an outbreak of multidrug-resistant *Pseudomonas aeruginosa* in a pediatric oncology unit.[7] Pathogen outbreak is a major concern in the healthcare setting, especially for resistant strains.[2,3] Is physical isolation a response to this worry? A randomized trial among patients with acute leukemia, performed in 1978, showed a decrease in fatal infections with increased survival among patients treated in a protected environment with prophylactic antibiotics.[8] However, even

in these early studies, the independent role of isolation versus antibiotic prophylaxis was not addressed, and the recognition of emerging antibiotic-resistant strains of bacteria when using antibiotics for patient protection rapidly became a worry.[9] Thus, available knowledge in this field is very limited and mostly derived from experience in patients undergoing HSCT, incorporating the use of laminar air flow (LAF) units, patient isolation units, prophylactic antibiotics, sterile and low-microbial diets, and antimicrobial decontamination.[10-13] Even in this setting, early prospective, randomized studies of protective environments among HSCT recipients suggested that LAF isolation and decontamination procedures resulted in a significant reduction in infections, but in no difference in survival, with most deaths a result of interstitial pneumonia or recurrent disease.[10] A retrospective study of the use of HEPA filtration units showed a reduction in the number of Aspergillus organisms in the air and a decrease in the risk of nosocomial Aspergillus infections.[14]

Current AIEOP standards

The AIEOP cooperative group has been working in pediatric hematology-oncology for about 40 years.[15] On the basis of the growing experiece in the treatment of children with cancer, constitutional or acquired bone marrow failure syndromes, or immune deficiencies, special attention has been paid to all measures aimed at reducing the risk for fatal infectious complications. Most of the effort has been aimed at developing pharmacological protocols for treatment or even prophylaxis of infections in the immune compromised host.[16] Cooperative protocols and guidelines for supportive therapy have been developed mostly as part of the chemotherapy treatment protocols. However, no special recommendations have been developed for non-pharmacological prophylaxis to date. As a general rule, isolation of patients at higher risk for infection, and in particular during HSCT, has been applied. During the mid 1980s, the use of LAF hoods became popular, especially among the larger centers.[13] Otherwise, no specific regulations or recommendations have been generated by the association. Thus, current policies in the over 40 AIEOP centers are based on local experience or attitudes. This prompted the group to address the issue of the opportunity to standardize the behaviors in the participant centers.

Measures aimed at protection of the patient

Overall, several issues have to be considered when trying to define if and which measures of non-pharmacological methods are indicated for prevention of infection in children undergoing chemotherapy. Available indications are sparse, mainly derived from observation of patients undergoing transplants, and never obtained through specific studies or even prospective data collection. Recommendations have focused on issues of ventilation, construction, room cleaning, isolation and barrier precautions, interactions with healthcare workers and visitors, skin and oral care, infection surveillance, and prevention of specific nosocomial and seasonal infections.

Table 1. Standard precautions.*

Handwashing (or using an antiseptic handrub)
• After touching blood, body fluids, secretions, excretions, and contaminated items
• Immediately after removing gloves
• Between patient contacts
Gloves
• For contact with blood, body fluids, secretions, and contaminated items
• For contact with mucous membranes and non-intact skin
Masks, goggles, face masks
• Protect mucous membranes of eyes, nose, and mouth when contact with blood and body fluids is likely
Gowns
• Protect skin from blood or body fluid contact
• Prevent soiling of clothing during procedures that may involve contact with blood or body fluids
Linen
• Handle soiled linen to prevent touching skin or mucous membranes
• Do not pre-rinse soiled linen in patient care areas
Patient care equipment
• Handle soiled equipment in a manner to prevent contact with skin or mucous membranes and to prevent contamination of clothing or the environment
• Clean reusable equipment prior to reuse
Environmental cleaning
• Routinely care, clean, and disinfect equipment and furnishings in patient care areas
Sharps
• Avoid recapping used needles
• Avoid removing used needles from disposable syringes
• Avoid bending, breaking, or manipulating used needles by hand
• Place used sharps in puncture-resistant containers
Patient resuscitation
• Use mouthpieces, resuscitation bags, or other ventilation devices to avoid mouth-to-mouth resuscitation
Patient placement
• Place patients who contaminate the environment or cannot maintain appropriate hygiene in private rooms

*Adapted from Ljungman *et al.*, 2009.

In an era of increasing financial constraints, recommendations on specific interventions that may turn out to be expensive and time-consuming need to be carefully revisited and, whenever possible, validated. Regarding this issue, it may be interesting to note that while the CDC/IDSA/ASBMT guidelines contain over 200 recommendations for infection control among HSCT recipients, only seven are supported by level I (randomized trial) evidence. Six recommendations hold clinical benefit and one is associated with harm. These level I recommendations do not include the use of patient isolation units, ventilation systems, construction or cleaning guidelines, skin or oral care, or the prevention of catheter-associated infections. The first AI recommendation (strongly recommended with randomized trial support) involves the long-held, low-technology, infection control practice of handwashing.[2] Guidelines for hand hygiene have been published, which specifically address issues of the indications for handwashing and antisepsis, the handwashing technique, surgical hand antisepsis, the selection of hand hygiene agents, and even healthcare worker educational and motivational programs.[17] However, a cross-sectional survey of university hospital physicians showed a dismal 57% average adherence.[18] Concerning the handwashing policy, the problem is how to improve this attitude and its compliance in the hospitals. Many studies suggest that the education and controls must be continuous, to highlight the attention of careworkers to this topic: easy, timely access to both hand hygiene and skin protection is necessary for satisfactory hand hygiene behavior. Alcohol-based hand rubs may be better than traditional handwashing as they require less time, act faster, are less irritating, and contribute to sustained improvement in compliance associated with decreased infection rates.[19] Whenever possible, local surveys on

Table 2. Transmission-based precautions are used when the route(s) of transmission is(are) not completely interrupted using standard precautions alone.*

Airborne precautions	Droplet precautions	Contact precautions
Used in addition to standard precautions for a patient known or suspected to be infected with microorganisms transmitted by the airborne route	Used in addition to standard precautions for a patient known or suspected to be infected with microorganisms transmitted by large-particle droplets (larger than 5 μm)	Used in addition to standard precautions for a patient known or suspected to be infected or colonized with microorganisms transmitted by direct contact with the patient or indirect contact with environmental surfaces or patient care items
Patient placement	**Patient placement**	**Patient placement**
Door closed Room air is exhausted to the outside (negative air pressure) using fan or other filtration system	Private room, door may be left open	Private room, door may be left open
If private room is not available, place patient in room with patient with active infection with the same disease, but with no other infection	If private room is not available, place patient in room with patient with active infection with the same disease, but with no other infection If neither option is available, maintain separation of at least 3 ft between patients	If private room is not available, place patient in room with patient with active infection with the same microorganism, but with no other infection
Respiratory protection	**Respiratory protection**	**Contact protection**
If TB is known or suspected, wear particulate respirator (if available) If chickenpox or measles: for immune persons, no mask is required; susceptible persons, do not enter room Remove PPE (face shield) after leaving the room and place it in a plastic bag or waste container with tight-fitting lid	Wear mask if within 3 ft of patient	*Gloving* Wear clean, nonsterile examination gloves when entering room Change gloves after contact with infective material (e.g. fecal materials or wound drainage) Remove gloves before leaving patient's room *Handwashing* Wash hands with antibacterial agent or use alcohol-based handrub after removing gloves Do not touch potentially contaminated surfaces or items before leaving the room *Gowns and protective apparel* Wear clean, nonsterile gown when entering patient's room if you anticipate contact with patient or if the patient is incontinent, has diarrhea, an ileostomy, colostomy, or wound drainage not contained by a dressing Remove gown before leaving room. Do not allow clothing to contact potentially contaminated surfaces or items before leaving room
Patient transport	**Patient transport**	**Patient transport**
Limit transport of patient to essential purposes only. During transport, patient must wear surgical mask Notify area receiving patient	Limit transport of patient to essential purposes only During transport, patient must wear surgical mask. Notify area receiving patient	Limit transport of patient to essential purposes only During transport, ensure precautions are maintained to minimize risk of transmission of organisms *Patient care equipment* Reserve noncritical patient care equipment for use with a single patient, if possible Clean and disinfect any equipment shared among infected and noninfected patients

*Adapted from Ljungman *et al.*, 2009.

Table 3. Empiric use of transmission-based precautions.*

Airborne	Droplet	Contact
Rashes (vesicle or pustule) Cough, fever, and upper lobe chest findings (dullness and decreased breath sounds)	Severe, persistent cough during periods when pertussis is present in community Generalized rash of unknown cause	Acute diarrhea in an incontinent or diapered patient Diarrhea with history of recent antibiotic use Bronchitis and croup History of infection with multi-resistant organisms Abscess or draining wound that cannot be covered

*Adapted from Ljungman *et al.*, 2009.

the compliance promoted by the hospital authority may support the continuous applications of these measures. The CDC/IDSA/ASBMT guidelines address an additional 12 recommendations graded AII (strongly recommended with well-designed non-randomized trial support). While the utility of specific isolation and barrier precautions have not been studied, a level AIII recommendation (strongly recommended with expert opinion support) is given to follow other published guidelines for hospital isolation and the prevention of nosocomial infections such as pneumonia or surgical site infections.[2]

Measures aimed at protection of contact persons, especially caregivers

All suggestions aimed at protecting caregivers are included in the universal precautions section.

Contact with animals and avoiding food-born infections

These issues were not addressed in the consensus.

Measures aimed at preventing transmission of specific agents according to their route of spread

A relevant issue may be the choice of which strategy we may want to adopt to prevent dissemination of specific infections according to their usual route of spread. Thus, additional infection control recommendations can be considered for epidemiologic factors such as the host, human-to-human interactions, fomites, air, food, water, soil, and construction and cleaning (Table 2). These precautions, which are aimed at limiting the spread of infectious agents and designed for avoiding specific infections, should be applied empirically, according to the clinical condition and the likely etiologic agents at the time, and then modified when either the pathogen is identified or a transmissible infectious etiology is ruled out (Table 3). The clinician's experience will direct specific restrictions for patients for whom multidrug-resistant bacterial strains or other potentially dangerous exposure(s) may reasonably be suspected.

Conclusions

In conclusion, despite the general attitude toward children undergoing chemotherapy, and particularly the practice of isolating them, there may be a wide range of inter-center variability. Most likely, isolation of individual children cannot be justified by currently available data, unless they have specific complications rather than uncomplicated fever of unknown origin. The use of air filtering or other environmental modifications, although possibly not incorrect, cannot be considered as the desirable standard of care. On the contrary, standard procedures, such as those suggested by CDC, appear warranted and definitely need to be enforced. As a paradigm, repeated and careful handwashing remains a pivotal behavior in limiting the horizontal spread of infectious agents among children in a pediatric hematology-oncology ward. As a result of the meeting, the expert opinion of AIEOP's panel recommends using a combined approach of standard and transmission-based precautions for children undergoing chemotherapy while additional, more sophisticated and expensive environmental procedures or structures cannot be considered as mandatory.

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