FLUCONAZOLE PROPHYLAXIS OF CANDIDA INFECTIONS IN PRETERM NEONATES

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Abstract

Infections belong to the most serious health problems in neonates. Invasive candidiasis is one of the leading causes of mortality and morbidity in Neonatal intensive care units (NICUs). A more cautious approach is adequate when dealing with fungal infections in premature neonates. Sometimes it is necessary to cure an infection at the very beginning just before manifestation of clinical symptoms. Neonatal colonization due to *Candida albicans* or non-*albicans* *Candidae* predisposes to invasive candidiasis. Pregnancies complicated by preterm delivery should be considered for screening and treatment of maternal *Candida* colonization to decrease the occurrence of neonatal fungal colonization and its consequences. It is important to prevent infection to spread among patients and avoid complications. Prophylaxis in neonates must be safe and effective. Most authors prefer selective prophylaxis. Fluconazole is the drug of choice for prophylaxis in extremely low birth weight (ELBW) neonates. The prophylaxis is beneficial especially in NICUs with high rates of invasive candidiasis. The authors describe benefits and trends in prophylaxis. They also summarize evidence on timing, dosing, and effect of fluconazole prophylaxis.

Key words: fluconazole, prophylaxis, candida, infection, neonate

INTRODUCTION

Invasive candida infection (ICI) in VLBW infants is a predominant cause of mortality and morbidity. In preterm infants, it is associated with a case fatality rate of approximately 30% and long-term neurodevelopmental impairment is common among survivors (1).

Treatment is often delayed because it is difficult to establish diagnosis early. Azoles are used as prophylaxis against invasive fungal infection in this population. Azoles are systemically absorbed antifungal agents and Fluconazole is the most commonly used agent. Widespread implementation of fluconazole prophylaxis has not been adopted because of limited results of randomized controlled trials and discrepancies in conclusions among authors.

Recent surveys show that only 30% to 50% of NICUs use some form of antifungal prophylaxis (2). Long term safety of antifungal agents and lack of a clear benefit on mortality have remained unresolved. At this time, prophylaxis is being used in NICUs individually, according to their own incidence of ICIs. Many studies show that antifungal prophylaxis for high-risk infants is an effective and safe possibility of infection prevention even in NICUs with a low incidence of ICI.

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There is an A-1 evidence supporting antifungal prophylaxis in high risk preterm infants confirmed by meta-analysis, Cochrane reviews, the American academy of pediatrics (AAP), and the Infection diseases society of America (IDSA) (3).

CANDIDA INFECTIONS

Invasive candida infections in neonates manifest as cutaneous form, bloodstream infection, urinary tract infection, meningitis, peritonitis, or as infection of any other sterile sites. As any other neonatal infection it is either congenital (early-onset) or nosocomial (late-onset). Incidence of ICI may increase as a result of the increased survival rate in ELBW infants. Candida infections contribute significantly to hospital costs in the high-risk NICU population (2).

Candida albicans and *Candida parapsilosis* are the two most common species of Candida (C) isolated in neonates. *C. glabrata*, *C. tropicalis*, *C. lusitaniae*, *C. guilliermondii* and *C. dubliniensis* are less common.

Pathogenesis and pathophysiology

Most Candida species are commensal organisms, being a part of the normal human microbiome of the skin and gastrointestinal tract. They become pathogenic, depending on the presence of risk factors, number of organisms and their virulence. Pathogenesis is influenced by transmission of the organism from a source, colonization and penetration of Candida through the host epithelial barriers resulting in dissemination. Transmission can be vertical from the mother or horizontal from people such as family members or healthcare workers or from the hospital environment.

Incidence

Candida infection is the third most common late-onset infection in VLBW infants (4). The incidence of invasive candidiasis in different studies and literature varies between 2.6–13.2% in VLBW neonates to 6.6-26% in ELBW neonates (5). The National Nosocomial Infections Surveillance system in USA evaluated 130,523 patients admitted to 128 NICUs in the period of 1995 - 2004. The incidence of candidemia per 1,000 patient-days increases with decreasing gestational age and birth weight as shown in Table 1 (4).

Table 1. Incidence of candidemia per 1000 patient-days (Hundalani, 2013)

Birth weight	Incidence of candidemia per 1000 patient-days
> 2,500 g	0.50
1,501–2,500g	0.42
1,001–1,500g	0.90
< 1,000g	3.51

Individual NICUs have reported the incidence of Candida infections in ELBW infants ranging from 4 to 30% (6). Across the world the rates of ICI vary among NICUs and it is possible that the various rates are due to differences in clinical practice such as use of the third-generation cephalosporines, steroids, and gastric acid reducing agents. Also feeding practices, infection control practices, and central line care policies contribute to this wide range of differences. Odds of invasive candidiasis can be as much as six times greater between two individual NICUs (6).

Risk factors

Risk factors of ICI are gestational age, birth weight less than 1,000 or 1,500g, use of broad spectrum antibiotics – especially the third-generation cephalosporines – for more than two days, presence of central venous line, respiratory support, parenteral nutrition, use of a histamine-2 blockers, systemic steroids, evidence of fungal colonization. One of the most important risk factors, is the immature immune system of premature neonates. Low levels of IgG, neutropenia, reduced opsonization, and reduced complement function are present in preterm infants. Candida like dermatitis, vaginal delivery, tendency to hyperglycaemia, and decreasing platelet count may also act as predictors of ICI. Gastrointestinal disease can be complicated by ICI, for example in patients with necrotizing enterocolitis, focal bowel perforation, and gastroschisis. Congenital heart disease increases the risk for ICI. In neonates on extracorporeal membrane oxygenation (ECMO) Candida is responsible for 10% of infections. (7). Breastfeeding can result in transmission of Candida to the infant's oral mucosa if there is Candida mastitis in the mother.

Colonization

Candida colonization occurs in 30-60% of infants admitted to the NICU (4). The possibility of ICI in colonized patients depends on risk factors. Newborns admitted to NICUs are at a great risk of nosocomial infections. The risk for nosocomial infection is associated with their susceptibility to infections as a result of both prematurity and invasive medical equipment necessary to survival (8). Candida species can be found as colonization on the skin, nasopharynx, periumbilical region, perineum, in gastric aspirate, and endotracheal secretion. Up to 60% of VLBW neonates may become colonized during the first month of stay in a NICU. About 85% of them acquire the fungus horizontally and 15% as a result of the maternal flora. For those who acquire nosocomial fungal infection, the peak manifestation period is the second and third week of life (9). Colonization by Candida species is a risk factor of invasive infection, so if the prophylaxis reduces colonization, it implies a benefit.

Manifestation of Candida infection

Cutaneous candidiasis commonly manifests as an erythematous maculopapular rash, skin erythema, pustules, vesicles, abscesses, and exfoliation. It covers one or more of the following areas: head, chest, abdomen, back, perineal area, or extremities (7). Congenital form can be seen on umbilical cord and placenta as white plaques.

Oral mucocutaneous Candida infection can be effectively treated with local antifungal therapy. Both forms are risk factors for developing invasive infection, especially in preterm infants.

Invasive Candida infection (ICI) is defined as a positive blood culture, cerebrospinal fluid, urine, ascites or pleural fluid, which are sterile body fluids, accompanied by at least two clinical signs of systemic inflammatory response. Candida infection in neonates most often presents as invasive bloodstream infection. Clinical presentation of invasive Candida infection is nonspecific. The most frequent presentation is similar to that of bacterial sepsis with lethargy, feeding intolerance, hyperbilirubinaemia, cardiovascular instability, or respiratory distress (10). ICI is often associated with renal failure, meningitis, or shock. Infection can originate from the skin and soft tissue, lung, gastrointestinal or urinal tract, central nervous system, or cardiovascular system. Intubated neonates may gain colonization of their upper respiratory tract. Candida may affect also the retina due to bloodstream infection. Endophthalmitis, osteomyelitis, or endocarditis develop rarely.

Diagnosis

Low platelets, coagulopathy, hypo- or hyperglycaemia, hyperbilirubinaemia, and elevated inflammatory markers can be seen in laboratory testing as nonspecific signs of Candida infection.

Microbiological testing for the presence of *Candida* from any part of the patient's body or from any body fluid can be performed. The small volume of blood sample for the microbiological testing may cause the under-diagnosing of ICIs as well as low sensitivity of current microbiologic diagnostic techniques. Molecular techniques with a higher sensitivity are being studied. Diagnostic techniques such as PCR, DNA sequencing, and hybridization techniques could allow rapid detection of *Candida*. The biomarkers of fungal disease such as β -glucan of the cell wall, anti-*Candida* antibodies (antimannan), candidal metabolites (D-arabinitol), and fungal chitin syntase can be more frequently used in the future (6). We detect *Candida* mannan and anti-mannan from blood in high risk VLBW neonates in our hospital.

Most commonly, an initial end-organ dissemination screen including an echocardiogram, abdominal ultrasound, cranial ultrasound, and ophthalmologic examination should be performed in patients with bloodstream infections (7).

Treatment and outcomes

In low and extremely low birth weight neonates ICI is associated with an attributable mortality rate of 30 to 40% (11). In a prospective multicenter study of extremely low birth weight infants over 30% of premature infants with candidiasis died prior to discharge, despite antifungal treatment. Moreover, 73% of the surviving infants experienced either neurodevelopmental impairment post infection or died at long-term follow-up (12). The mortality rate usually reported is approximately 20% but it can reach up to 40% (13). Premature infants with invasive candidiasis are more likely to develop periventricular leukomalacia, retinopathy of prematurity, and chronic lung disease (6).

Adequate dosing of antifungal therapy has been understudied in neonates and remains a critical issue (7). We use dosing according to Martin et al. as shown in table number two in our NICU.

Table 2. Antifungals to treat invasive *Candida* infection (Martin, 2015)

Antifungal	Dose	Interval	Comments
Amphotericin B deoxycholate	1.0–1.5 mg/kg	Every 24 hours	Monitor electrolytes
Amphotericin B lipid formulations	5–7 mg/kg	Every 24 hours	
Fluconazole	12 mg/kg	Every 24 hours	Monitor liver function tests
Caspofungin	2.5–3 mg/kg	Every 24 hours	Monitor electrolytes, calcium, phosphorus and liver function tests
Micafungin	7–10 mg/kg	Every 24 hours	Monitor liver function tests
Anidulafungin	3 followed by 1.5 mg/kg	Every 24 hours	Monitor liver function tests

Antifungal Prophylaxis

Clinical trials of antifungal prophylaxis have primarily focused on the use of fluconazole which is administered either intravenously or orally. Other possibility is to use nystatin or miconazol but those are local antifungal agents that are not adequately absorbed in the gastrointestinal tract. The choice of an antifungal agent should be influenced by an individual evaluation of the patient and also by the local NICU epidemiology and relative cost of the treatment.

The high risk of ICI persists from birth to 3 month, with the highest risk reported to be between 11 and 30 days of life. The approach of prophylaxis lasting 4 to 6 weeks of life to all ELBW infants treats a large number of infants. Some of them may be at a low risk for infection (14). Therefore, recently a targeted prophylaxis is preferred and it reduces the incidence of ICI while minimizing drug exposure.

Within the last five years many studies have been carried out and published on the prophylactic use of fluconazole in VLBW neonates. Especially the neonates hospitalized in NICUs, who require the use of invasive procedures, mechanical ventilation, parenteral nutrition by means of central venous catheters, and antibiotic or steroid therapy, are seriously immunocompromised and, therefore, at the greatest risk for developing ICI. Several authors demonstrated reduced incidence of ICI after antifungal prophylaxis administration. However, the incidence of neonatal infections including ICIs decreased lately due to improvements in perinatal and neonatal care. Many centers have reported dramatic decrease in overall bloodstream infection incidence through the use of bundles for central line insertion; maintenance dedicated line-care personnel and increased use of breast milk for enteral nutrition (6).

Despite evidence and recommendations favoring the use of intravenous fluconazole for invasive fungal infections prevention in neonates, universal use of antifungal prophylaxis is controversial according to the literature data. The dosing, dosing frequency of fluconazole, and also the indication criteria vary.

Rolnitsky (2012) published a protocol for fluconazole prophylaxis in Israel. The protocol contains major and minor criteria. Presence of any major criteria or any of two minor criteria results in indication for prophylaxis. The major criteria include birth weight $\leq 1,000$ grams, corrected gestational age of ≤ 28 weeks, broad-spectrum antibiotics (not initial ampicillin and gentamycin therapy). Minor criteria are respiratory support, inotropics, parenteral nutrition, recent NEC or abdominal surgery, central venous catheters, corticosteroids, proton pump inhibitors, or H2 blockers (15).

A dosing regimen of 6mg/kg twice a week is adequate when intravenous fluconazole is used for prophylaxis (6).

Since 2009 the fluconazole prophylaxis was recommended in NICUs with fungal infections rates higher than 5%. Later, the Infectious Diseases Society of America (IDSA) stated that prophylaxis for invasive candidiasis with fluconazole can be considered in VLBW newborns in NICUs with rates of candidiasis higher than 10%, based on placebo controlled randomized trials (13).

Latin America Invasive Mycosis Network (2013) recommends prophylaxis with fluconazole 3mg/kg twice a week within six weeks in ELBW neonates who are in NICUs with high incidence of invasive candidiasis (IC) up to 5%. The use of prophylaxis should be considered individually according to the risk factors of each newborn in NICUs with a lower incidence (16).

The European Society of Clinical Microbiology Infectious Diseases recommends antifungal prophylaxis in neonates considering risk stratification strategy as follows:

- a.) fluconazole 3–6mg/kg twice a week intravenously or orally is indicated in all VLBW infants in NICUs with high frequency of IC over 5%
- b.) the decision to use fluconazole prophylaxis should be made individually in NICUs with incidence rates lower than 2% (13).

Data on fluconazole prophylaxis

Aliaga et al. examined data from 709,325 neonates at NICUs in the period of 1997 and 2010. The data were collected prospectively from daily progress notes generated by the clinicians. The authors identified 2,101 episodes of ICI. Fluconazole prophylaxis use increased during the study. The annual incidence of ICI decreased among all infants. The decrease in incidence was from 24.2 to 11.6 episodes per 1,000 patients in infants with birth weight of 750–999 grams, and from 82.7 to 23.8 episodes per 1,000 patients in infants less

than 750 grams. Mortality was higher in infants with ICI compared to those without ICI (19.9% vs. 2.1%; $p < 0.001$) (5).

Kaufman D. A. et al. (2014) collected data retrospectively from the database of a placebo controlled randomized clinical trial. 2017 infants with a median birth weight of 737 grams and gestational age of 25 weeks were enrolled in this study; the infants were NICU patients in the United States and Canada. Fluconazole prophylaxis was used in 17 of 95 sites during the study, which represents 18%. Fluconazole prophylaxis was administered for 20 to 48 days. Dosing varied from 3mg/kg to 6mg/kg either twice a week or more frequently. ICI occurred in 0.8% fluconazole prophylaxis patients compared to 7.3% of control infants ($p = 0.006$). Incidence of adverse effects was similar in both prophylaxis and placebo group and there was no difference in overall mortality and morbidity (3).

Authors from Turkey found out in their observational pre-post cohort study in ELBW neonates who were given prophylactic fluconazole 3mg/kg twice a week that there was no fungal infection in prophylactic group compared to control group. There were no significant differences between these two groups in mortality rates and no adverse reactions during the prophylaxis period (17).

Oral nystatin, intravenous fluconazole, and intravenous amphotericin B have all been considered as suitable drugs for prophylactic use in the population of preterm infants. Fluconazole has emerged as the best choice for chemoprophylaxis in premature infants (18).

In the same year Benjamin DK et al. (2014) published a randomized, blinded, placebo-controlled trial of fluconazole prophylaxis in ELBW infants. Their findings do not support the universal use of prophylaxis because prophylaxis compared to placebo did not result in a lower incidence of ICI or mortality (19). However, their study group consisted of only 362 infants compared to other larger trials which are supporting the use of prophylaxis.

According to Kirpal et al. (2016) the incidence of ICI in WLBW infants was significantly lower in the fluconazole group compared to the control group: 21% compared to 43.2% with CI 95 % and $p < 0.05$. It is interesting that there was also significantly lower fungal attributable mortality in the fluconazole group compared to the control group: 2.6 % versus 18.9% with CI 95% and $p < 0.05$ (20).

The Cochrane review published by John Wiley and sons in 2015 identified 15 trials enrolling all together 1,690 neonates. Ten trials (1371 infants) compared systemic antifungal prophylaxis versus placebo or no drug. These trials were generally of good methodological quality. Meta-analysis found a statistically significant reduction in the incidence of invasive fungal infection. The average incidence of invasive fungal infection in the control groups of the trials (16%) was much higher than that generally reported from large cohort studies. Meta-analysis did not find a statistically significant difference in the risk of death prior to hospital discharge. Very limited data on long-term neurodevelopmental outcomes were available. Three trials that compared systemic versus oral or topical non-absorbed antifungal prophylaxis did not detect any statistically significant effects on invasive fungal infection or mortality. Two trials that compared different dose regimens of prophylactic intravenous fluconazole did not detect any significant differences in infection rates or mortality (21).

Ericson et al. (2016) published a meta-analysis of all randomized placebo-controlled trials conducted in the United States. They compared infants treated with fluconazole to infants whom was given placebo. Four of six trials demonstrated a decreased incidence of ICI in infants treated with fluconazole. Remaining two trials found similar incidence of ICI but lower frequencies of Candida colonization in infants treated with fluconazole. In the survival analysis the infants who received fluconazole prophylaxis also had a lower cumulative incidence of the composite outcome of death or invasive candidiasis through the end of the evaluation period ($p < 0.001$). Clinical safety events were similar (22).

The same year Che, Zhou and Wu (2016) published a meta-analysis of five randomized controlled trials since 2001 from PubMed and EMBASE involving 1,006 neonates. Prophylaxis with fluconazole resulted in a significant reduction in ICI ($p = 0.0179$) (23).

Rios et al. published a review covering research at databases: PubMed, Capes Portal, Virtual Health Library Lilacs, Scopus, and Cochrane. Considering 168 articles the authors stated that there was a statistically significantly lower frequency of invasive candidiasis in the groups receiving prophylactic fluconazole compared to placebo or no prophylaxis groups in eleven of twelve items (13).

Abou Jaode et al. (2013) from the USA published a retrospective study on fluconazole prophylaxis for the period of 2007–2011, their study group consisted of neonates with birth weight less than 900 grams. Interestingly, they found that the incidence of coagulase-negative *Staphylococcus* decreased from 46.2% to 24.7% after the institution of fluconazole prophylaxis (24).

Nystatin

Nystatin is a nonabsorbent antifungal agent given prophylactically usually 3 to 4 times per day over several weeks. Successful use of nystatin as the oral antifungal prophylaxis in 33 infants with birth weight below 1,250g was first published in 1988 by Sims et al. The authors declared a decreased incidence of ICI.

Oral nystatin prophylaxis was associated with a decrease in *Candida* bloodstream infections and meningitis by 56% in VLBW and 57% in ELBW infants as documented in the epidemiologic study of 14,778 VLBW infants in Australia and New Zealand within the period of 1993–2006 (25).

Nystatin prophylaxis in VLBW infants was associated with a reduction in the incidence of invasive candidiasis from 14 to 2 % when compared with no intervention (26).

Oral nystatin is less costly than fluconazole for intravenous administration, but when given more times a day (per os) compared to twice weekly (i.v.), the final cost of the oral drug is higher. Although both nystatin and fluconazole are efficacious in preventing ICI, the evidence favors fluconazole because of its higher efficacy 80–90% vs. 50–60% (2).

Data on reduction in risk of invasive fungal infection in very low birth weight infants treated with oral/topical non-absorbed antifungal prophylaxis should be interpreted cautiously because of methodological weaknesses in the included trials. Further large randomized controlled trials in current neonatal practice settings are needed to resolve this uncertainty. These trials might compare oral/topical non-absorbed antifungal agents with placebo, with each other, or with systemic antifungal agents and should include an assessment of effect on long term neurodevelopmental outcomes (27).

Fluconazole

Fluconazole is used commonly in neonatal practice and appears to be a safe treatment for newborn infants. Its use as antifungal prophylaxis in VLBW neonates was reported for the first time in 2001. First trials demonstrated a decrease in colonization and following several publications demonstrated decrease in ICI and also in colonization by *Candida*. However, no significant reduction in mortality had been observed.

Fluconazole is the first generation triazole. It inhibits 14- β -sterol demethylase of the cytochrome P450 system which is necessary for the production of ergosterol, a major component of the fungal cell membrane. Intravenous infusions are given over sixty minutes. Pills and oral suspensions are also available. The suspensions are well absorbed with oral bioavailability approximately 90%. Fluconazole achieves a good penetration into the cerebrospinal fluid and lungs. It is excreted unchanged into the urine. It has a long half-life and a low lipophilicity and protein-binding properties (9). Fluconazole is bound minimally to plasma proteins (12%) (28).

The most frequently reported side effects of fluconazole treatment are a transient elevation of plasma levels of creatinine and hepatic enzymes and skin rash. There have also been reported adverse events such as Stevens-Johnson syndrome, anaphylactic shock, and lengthening of the electrocardiogram's QT interval. Adverse effects of fluconazole include liver and renal dysfunction, cholestasis, skin rash, rickets, or developmental morbidities

such as cerebral palsy, blindness, deafness, catch-up growth failure. Some studies have suggested an increased risk of cholestasis related to fluconazole prophylaxis (29). However, a subsequent study by the same authors concluded that fluconazole prophylaxis administered twice weekly was not associated with the increased incidence of cholestasis as they reported initially (30). Additionally, there is a potential risk of adverse effects as a result of drug interactions with medications prescribed to newborn infants, including cisapride, theophylline, and thiazide diuretics.

An important problem related to common use of fluconazole may be the increasing incidence of fluconazole resistant *Candida* species such as *C. krusei* and *C. glabrata*. In addition, a negative correlation has been found between fluconazole consumption and the rate of *C. parapsilosis* bloodstream infections (30). But in the same year Ericson et al. published the results of their meta-analysis concluding that fluconazole prophylaxis has no impact on *Candida* strains resistance. The National Nosocomial Infections Surveillance System of the United States has demonstrated decreases in the incidences of candidemia and ICI due to *Candida albicans* and *Candida parapsilosis* in ELBW infants and no changes in the incidences of infections involving other *Candida* species referring to a period of 10 years (31).

The usual dose of prophylactic intravenous fluconazole is 3 or 6 mg/kg. The dosing interval varies from 24 to 72 hour and the duration of prophylaxis varies from 2 to 6 weeks of age. Most NICUs start the prophylaxis on the third day of life or on the third day of antibiotics treatment and the prophylaxis continues until 4 weeks or until the end of the presence of defined risk factors. There is a report that demonstrates the superior efficacy when starting antifungal prophylaxis prior to colonization, within 48 hours after birth (26). Delaying antifungal prophylaxis until colonization has been assessed, it is being 30% less effective than if starting within 72 hours after birth (9).

If fluconazole is being used for prophylaxis, a different antifungal should be used for treatment in the NICU, for example the second-generation triazole, voriconazole, or amphotericine B. Echinocandins (micafungin, caspofungin) and nucleoside analogues (flucytosine) are recommended less frequently.

A very important issue is the cost of ICI treatment. However, there was only one study published on hospital costs in the neonatal population. Smith et al. found that additional hospital cost due to ICI was between 16,996 and 39,897 dollars, median was 28,446 dollars (2). There is no study on the costs associated with morbidity due to ICI.

CONCLUSION

Antimycotic prophylaxis is the most effective way to prevent invasive candida infections in ELBW neonates. Antifungal prophylaxis can be administered intravenously, orally, or topically. Incidences of ICI in the NICU and risk factors in the neonate have to be considered when indicating the prophylaxis. The reduction in ICI incidence has been confirmed by many studies of good quality. According to the trials it can be stated that it is safe and has a cost risk benefit in neonates at intensive care units Fluconazole is the recommended antimicrobial agent for antifungal prophylaxis. It is widely available, well tolerated, and not expensive.

Fluconazole prophylaxis in ELBW neonates should be targeted and used in NICUs with baseline rates of invasive candidiasis higher than 5%. Selective prophylaxis decreases the number of treated infants and time of exposure to fluconazole and there is a potential benefit of reducing the risk of developing *Candida* strains resistant to fluconazole.

According to the evidence the decrease in the incidence of ICI depends significantly on the ICI incidence in the control group. The higher the incidence of ICI is in the control group, the more effective the prophylaxis is in decreasing the number of ICI.

Even if the total mortality rate was not significantly decreased by fluconazole prophylaxis in VLBW neonates, *Candida* related mortality was decreased significantly.

Prevention strategies of *Candida* infections also include more effective infection control, strict hand-washing, eager response to suspected infections, new, faster diagnostic methods, and improved management of maternal infections during pregnancy. Moreover, isolation of infected patients excludes infection transmission from one patient to another.

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