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Original Article

ANTIBIOTIC RESISTANCE PATTERN OF BACTERIAL PATHOGENS IN THE NEONATAL INTENSIVE CARE UNIT OF SOHAG UNIVERSITY HOSPITAL

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ABSTRACT

Background: Antimicrobial-resistant pathogens are of increasing concern in the neonatal intensive care unit population. A myriad of resistance mechanisms exist in microorganisms and management can be complex because broad-spectrum antibiotics are increasingly needed.

Objective: To study the bacterial pathogens causing neonatal sepsis and their sensitivity pattern so that guidelines can be prepared for empirical antibiotic therapy.

Setting: The study was conducted in the neonatal intensive care unit (NICU) of sohag university hospital in the period between August 2010 and August 2012.

Methods: Blood specimens for culture were drawn from 330 newborns admitted in the NICU of Sohag University Hospital. The specimens were inoculated into WAMPOLE ISOLATOR 1.5. The antibiotic susceptibilities of the isolates were determined by the disk diffusion method on Mueller–Hinton agar plates using calibrated inoculum of the isolates based on McFarland turbidity standard according to the Clinical Laboratory Standards Institute. The antibiotic resistance pattern of the isolates was studied by modified Kirby Bauer disc diffusion technique as well as E test.

Results: A total of 117 organisms were isolated. These included Klebsiella pneumoniae accounted for (23.07%) of the total isolates followed bycoagulase negative Staphylococci(CoNS) which accounted for (17.94%), then Pseudomonas aeruginosa (15.38%), followed by Staphylococcus aureus which accounted for (12.82%), while Esch. coli accounted for (10.25%), then Enterococcus faecalis and Burkholderia cepacia each accounted for (7.69%), finally Streptococcus pyogenes with a percentage of (5.12%). Most bacterial isolates were sensitive to imipenem and some isolates were sensitive to fourth-generation cephalosporins, but most isolates were highly resistant to the majority of other antibiotics tested. Pseudomonas aeruginosa and Burkholderia cepacia have shown the highest rate of antibiotic resistance, while Streptococcus pyogenes has shown the least resistance. Phenotypic prevalence of extended spectrum beta lactamase (ESBL) producing gram negative bacteria was 75%, while Prevalence of Methicillin resistant Staphylococcus aureus (MRSA) 80%, Prevalence of methicillin resistant coagulase negative Staphylococci (MRCoNS) 78% and Prevalence of vancomycin resistant enterococci(VRE) was found to be 33%.

Conclusion: Control and prevention of antibiotic-resistant organisms require an interdisciplinary team with continual surveillance. Judicious use of antibiotics; minimizing exposure to risk factors, when feasible; and effective hand hygiene are crucial interventions to reduce infection and transmission of antibiotic resistant organisms (AROs).

Keywords: *Antibiotic resistance, Neonatal intensive care unit.*

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INTRODUCTION

Neonates represent one of the highest risk groups of hospitalized patients for the development of sepsis, with up to 50% of neonatal intensive care unit (NICU) patients experiencing one or more episodes of sepsis. Neonatal sepsis is an important cause of immediate morbidity and mortality as well as being associated with an increased risk of long-term neurological sequelae and is also a major contributor to additional health care costs *(Heron, 2010)*.

Neonatal sepsis is classified as early onset neonatal sepsis (EONS) or late-onset neonatal sepsis (LONS). Whereas early-onset neonatal sepsis is usually due to microorganisms that are acquired from the mother ante partum or intrapartum, the pathogens causing late-onset sepsis (LONS) are generally acquired from the postnatal environment. LONS is most important as a nosocomially acquired infection in hospitalized babies. The timing of the transition from EONS to

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LONS is not clear-cut and depends, to some extent, on the individual pathogen *(Stoll et al. 2011)*.

Most studies of risk factors for LONS have been based on the US CDC definition of a nosocomial infection being one that presents 48h or more after admission. However, some authors have found that the transition from maternal to nosocomial origin of infection may begin even earlier than this and have proposed that only very early-onset infections presenting within the first 24h should be regarded as unequivocally of maternal origin *(NNISS, 2011).*

The spectrum of organisms causing neonatal sepsis has changed over time, since the late 1960s to early 1970s, group B Streptococci (GBS) has emerged as a major pathogen associated with neonatal sepsis and meningitis. Many infants with invasive GBS disease present with early-onset sepsis and are often identified and treated before discharge after birth *(Vergnano et al. 2005)*.

Other Gram-positive organisms causing disease in young infants include Staphylococcus aureus, Enterococcus species, Streptococcus pneumoniae and less frequently, Listeria monocytogenes. The most commonly isolated bacterial organisms in neonates are Gram-negative organisms and Klebsiella pneumoniae is the most common Gram-negative organism found in infants presenting with fever. Other Gram-negative organisms include Esch. coli,Enterobacter species, Salmonella, Citrobacter species and Neisseria species *(Byington et al. 2012)*.

Since the early ninties the subject of the emergence and subsequent increase in the incidence of resistance to antimicrobial agents has become a serious threat. Reports from all around the world suggest that antibiotics are rapidly losing their effectiveness, with some early reports going so far as to suggest that we are approaching a post-antibiotic era *(Cohen, 1992)*.

Antimicrobial resistance is increasing for a variety of reasons, these include suboptimal use of antimicrobials for prophylaxis and treatment of infection, prolonged hospitalization, increased number and duration of intensive-care-unit stays, multiple co-morbidities in hospitalized patients, increased use of invasive devices and catheters, ineffective infection-control practices, noncompliance with infection-control practices, transfer of colonized patients from hospital to hospital, grouping of colonized patients in long-term-care facilities, antibiotic use in agriculture, and increasing national and international travel *(Diekema et al. 2004)*.

Infection with resistant organisms in neonates has been associated with treatment failure, higher morbidity and mortality and increased costs. It is well noticed that the multi - drug resistance of the causative organisms of neonatal sepsis is a rapidly emerging and potentially disastrous problem *(Zaidi et al. 2009)*.

MATERIAL AND METHODS

Study Population: This study was carried out at the neonatal intensive care unit of Sohag University Hospital in the period between August 2010 and August 2012. Blood samples for culture were drawn from 330 newborns (5-28 days) with clinical manifestations of sepsis including (Hyperthermia or hypothermia, Failure to feed, Respiratory distress, Lethargy , hypotonia, Irritability, Vomiting, Seizure, Abdominal distension and Diarrhea). The following variables were recorded: mode of delivery, gestational age, birth weight, age, sex and outcome. Written informed consent was obtained from the newborns parents/guardians.

Sample Collection, Handling and Transport: Using aseptic technique by applying povidone iodine for 3 times in one direction followed by 70% alcohol also for 3 times in the same direction at the site of vein puncture, 0.5-1 ml venous blood was drawn from the femoral vein by the attending nurse and drawn into WAMPOLE ISOLATOR 1.5 (OXOID Ltd, Wade Road, Basingstoke, UK) and processed using the centrifugation lyses method.

Culture and Identification: Subcultures were made conventionally on plates of sheep blood agar, chocolate agar, MacConkey´s agar and Sabouraud´s dextrose agar (OXOID Ltd, Wade Road, Basingstoke, UK) with aerobic incubation for blood, MacConkey's and Sabouraud`s and anaerobic incubation for chocolate agar at 37°C for 18–24 hours. The isolates were identified by Gram stain, commercial biochemical identification systems usingMICROBACT 24E (OXOID Ltd, Wade Road, Basingstoke, UK) for gram negative bacilli isolates and API 20 STREP (BioMerieux, Marcy l` Etoile, France) for Streptococci, other isolates wereidentified using other specific methods, as mannitol salt agar for isolation of S. aureus, coagulase test for differentiating coagulase negative staphylococci (CoNS), catalase test for differentiating Streptococcifrom other gram positive cocci.

Antibiotic Sensitivity Testing: The antibiotic susceptibilities of the isolates were determined by the disk diffusion method on Mueller–Hinton agar plates using calibrated inoculum of the isolates

based on McFarland turbidity standard according to (the Clinical Laboratory Standards Institute *(CLSI, 2010)*. Antibiotic resistance pattern of the isolates was studied by Modified Kirby Bauer disc diffusion technique as well as E test.

The sensitivity of Gram negative isolated bacteria to the following antibiotics was tested: (OXOID Ltd, Wade Road, Basingstoke, UK). Ampicillin (10 µg), Ampicillin/ sulbactam (20 µg), Cefotaxime (30 µg), Ceftriaxone (30 µg), Cefepime (30ug), Ceftazidime (30 µg), Piperacillin/tazobactam (110 µg), Amoxicillin/Clavulanic acid (30 µg), Aztreonam (30 µg).

The sensitivity of Gram positive isolated bacteria to the following antibiotics was tested: (OXOID Ltd, Wade Road, Basingstoke, UK).Penicillin G (10 µg), Rifampicin (5 µg), - Erythromycin (15 µg), - Vancomycin (30 µg), Clindamycin (2 µg), Oxacillin (1 µg), Linezolid (30 µg) .

The sensitivity of both Gram positive and negative bacteria to the following antibiotics was tested: (OXOID Ltd, Wade Road, Basingstoke, UK). Trimethoprim–sulfamethoxazole (25 µg), Imipenem (10 µg), Meropenem (10g), Gentamicin (10 µg), Kanamycin (30 µg), Cefoperazone/ sulbactam (105 µg).

Multiple drug resistance of the isolated bacteria was tested as follows:

- For Methicillin resistant Staphylococcus aureus (MRSA) and Methicillin resistant CoNS (MRCoNS) disk diffusion test with an oxacillin disk (1 µg) (OXOID Ltd, Wade Road, Basingstoke, UK) was used.
- For extended spectrum beta lactamase producing gram negative bacilli (ESBL) double disc synergy test was used.
- For Vancomycin Resistant Enterococci (VRE) vancomycin E test was used.

Statistical Analysis:
Data was analyzed using STATA intercooled version 9.2. Quantitative data was analyzed using student t-test to compare means of two groups and ANOVA for comparison of the means of three groups or more. Qualitative data was compared using Chi square test. P value was considered to be significant if it was less than 0.05.

RESULTS

Risk Factors Associated with Blood Culture Proven Neonatal Sepsis: Risk factors associated/ not-associated with blood culture proven sepsis are outlined in Table (1). Among those, male gendre, preterm neonates (P value < 0.0001), neonates with low birth weights (P value <0.0001), delivered vaginally and those with I/T(immature to total neutrophil) ratio ≥0.2 (P value < 0.0001) were at risk in developing culture proven nosocomial LONS.

Antimicrobial Susceptibility:

A) Gram negative bacteria:
The resistance patterns of gram-negative bacteria (n=66) isolated from the septic neonates against 14 antibiotic are presented in Table (3). High level of resistance (>80%) was observed to Ceftriaxone, Ceftazidime, Cefotaxime, Amoxicillin/ Clavulanic acid and Kanamycin, intermediate level of resistance (60-80%) was observed to Ampicillin/ sulbactam, Gentamicin, Cefepime and Low level of resistance (<60%) was observed to Trimethoprim-sulphamethoxazole, Piperacillin/tazobactam, Cefoperazone /sulbactam, Aztreonam, Imipenem and meropenem.

B) Gram positive bacteria:
The susceptibility patterns of gram-positive bacteria (n=51) isolated from septic neonates against 12 antimicrobial agents are presented in Table (4). high level of resistance (>80%) was observed to Gentamicin, intermediate level of resistance (60-80%) was observed to Penicillin and Low level of resistance (<60%) was observed to Cefoperazone /sulbactam, Clindamycin, Trimethoprim-sulphamethoxazole, Rifampicin, Vancomycin, Erythromycin, oxacillin and and Linezolid, all isolates were sensitive to Imipenem, Meropenem,

In general imipenem and Meropenem was the most effective drugs against the tested gram-positive and gram-negative bacteria.

C) Multi-Drug Resistance (MDR):
Multiple resistance (resistance to two or more drugs) was observed in 36/51 (70.58%) and 56/66 (84.8%) gram positive and gram negative bacteria respectively (p<0.05). Among the gram positives, MDR was observed among Staphylococcusaureus,coagulase negative staphylococci and Enterococcus faecalis, while among the gram negatives, MDR was observed in Klebsiella pneumoniae. Pseudomonas aeruginosa, Burkholderia cepacia and Escherichia coli.

Prevalence of ESBL producing Gram negative bacilli(phenotypically detected) was observed to be 75%.

Prevalence of MRSA (phenotypically detected) was observed to be 80%. Prevalence of VRE (phenotypically detected) was observed to be 33%.

Prevalence of MRCoNs (phenotypically detected) was observed to be 78%.

Table 1: Risk Factors associated with Blood Culture Proven Neonatal Sepsis.

Variables	Culture positive (n=117) NO %	Culture negative (n=213) NO %	P value
Gendre: Male Female	 67 33	 29 71	<0.0001
Gestational age: <37 weeks (preterm) 37-42weeks (full term) >42 weeks (post-term)	 58 42 0	 26 74 0	<0.0001
Weight at birth 1500-2500g (LBW) 2500-4000g (normal) >4000g (overweight)	 75 25 0	 0 48 52 0	<0.0001
Mod of delivery Normal vaginaldelivery Caeserian section	 67 33	 65 35	<0.0001
I/T ratio ≥0.2 <0.2	 58 42	 30 70	<0.0001

Table 2: Types of bacteria isolated:

Organism	No.	(%)
Klebsiella pneumoniae	27	(23.08)
CoNS	21	(18)
Pseudomonas aeruginosa	18	(15.38)
Staph. Aureus	15	(12.08)
Esch- coli	12	(10.26)
Burkholderia cepacia	9	(7.69)
Enterococcus faecalis	9	(7.69)
Strept. Pyogenes	6	(5.13)
Total	**117**	**(100.00)**

Table 3: Pattern of antibiotic resistance of the isolated Gram negative bacteria.

Antibiotics	% of Resistance			
	Klebsiella pneumoniae	Pseudomonas aeruginosa	Esch. coli	Burkholderia cepacia
Ampicillin/sulbactam	100.00	100.00	25.00	100.00
Ceftriaxone	85.71	100.00	100.00	100.00
Cefotaxime	100.00	100.00	100.00	100.00
Ceftazidime	100.00	100.00	100.00	100.00
Cefepime	57.14	66.67	25.00	67.00
Cefoperazone/sulbactam	28.57	16.67	25.00	100.00
Amoxicillin/Clavulanic acid	85.71	60.00	40.00	50.00
piperacillin/tazobactam	28.57	16.67	45.00	33.33
Gentamicin	71.43	33.33	50.00	100.00
Kanamycin	100.00	100.00	100.00	100.00
Aztreonam	27.00	20.00	25.00	33.33
Trimethoprim/sulphamethoxazole	28.57	66.67	50.00	66.67
Imipenem	14.29	20.00	0.00	33.33
Meropenem	14.29	16.67	25.00	66.67

Table 4: Pattern of antibiotic resistance of the isolated Gram positive bacteria.

Antibiotics	% of Resistance			
	Staph. aureus	Enterococcus faecalis	CoNS	Strept. pyogenes
Penicillin	100.00	100.00	100.00	0.00
Oxacillin	80.00	100.00	77.88	0.00
Vancomycin	10.00	33.33	0.00	0.00
Gentamicin	80.00	100.00	0.00	100.00
Erythromycin	80.00	100.00	22.22	70.00
Clindamycin	60.00	66.67	0.00	0.00
Linezolid	00.00	09.00	0.00	0.00
Trimethoprim/sulphamethoxazole	100.00	100.00	22.22	0.00
Cefoperazone/Sulbactam	80.00	100.00	0.00	0.00
Imipenem	0.00	0.00	0.00	0.00
Meropenem	0.00	0.00	0.00	0.00
Rifampicin	40.00	33.33	0.00	0.00

DISCUSSION

In our study out of 330 newborns with suspected nosocomial neonatal sepsis 117(36%) were positive for bacterial culture which is in agreement with the reports from other developing countries e.g. India (34%) *(Madhu et al. 2002)*, Uganda (37.5%) (Mugalo et al. 2006) and Bangladesh (30%) *(Naher et al. 2011)*, Others reported higher results e.g. Saudi Arabia (61%) *(Dawodu et al. 1997)*, Pakistan (58%), *(Aftab & Iqbal, 2006)*, Libya (69%) *(Misallati et al. 2000)*, Egypt (50%) *(Moore Kelly et al. 2005)*, Nigeria (45.9%) *(Meremikwu et al. 2005)*, India (52.6%) *(Murty & Gyaneshwari, 2007)*, Indonesia(65.3%) *(Rohsiswatmo, 2006)* and Georgia (63%) *(Macharashvili et al. 2009)*.

Lower isolation rates were reported in previous studies conducted in other developing countries e.g. in Iran (6.6%) *(Movahedian et al. 2006)* , Kuwait (8.7%) *(Huda et al. 2001)* and Saudi Arabia (5%) *(Alumran & Twum-Danso, 1997)*. These variations can be attributed to many different factors,with antibiotic therapy prior to laboratory diagnosis being the most important influence on the low culture results.

In the present study, males showed higher blood culture positive results than females, which is similar to the findings reported by others *(Ravi, 2007)*, but disagree with studies from India *(Salamati et al. 2006)* and Yemen *(Hassan et al. 2012)* who reported higher positive results in females than males. There was a significant correlation between low birth weight and the incidence of neonatal sepsis. The same finding was observed by other workers *(Jaswal et al. 2003)*.

In Our study preterm neonates represented (74%) of those with positive blood culture while full term neonates represented (26%) and (42%) of those with negative blood culture were preterm and (58%) were full term. Similar reports have been made by others *(Murphy et al. 2001)*.

Many researchers related cesarean section to some morbidities and to mortality *(De Luca et al., 2009)* while others demonstrated its protective effect *(Mondal, 1991)*, which in agreement with our study.

Mortality rate among positive blood culture cases in this study was 41%, which is higher than that found by other workers *(Andad, 1991)* reported 30%, but lower than that found previously in Egypt *(Moore et al. 2005)*.

The most common organisms isolated in the present study were Gram negative bacteria. This is in agreement with other related studies in many developing countries *(Waseem et al. 2005)*, but disagree with those reported in Kuwait *(Huda et al. 2001)*, in the UK *(Hyde et al. 2002)* and in the USA *(Mehdinejad et al. 2009)* where Gram positive bacteria were predominant.

K. pneumoniae was the predominant isolate in the present study, representing (23%) of the total isolates. Similar findings were reported in Georgia *(Macharashvili et al. 2009)* and India (Kumhar et al. 2002), but lower results were reported from Nepal (18.3%) *(Shaw et al. 2007)* and Pakistan (7.6%) *(Rahman et al. 2002)*, Moreover, it was found in this study that Pseudomonas species were the second most common Gram negative isolate; similar findings were reported in Pakistan *(Rahman et al. 2002)* and India *(Pawa et al. 1997)*. The majority of Gram negative organisms, isolated in this study and in other studies, suggest that these infections may in fact be acquired from the hospital environment, due to poor hygienic practices during caring of the newborns *(Gupta et al. 2004)*. Another possible explanation of the predominance of Gram negative bacteria in our study is that asymptomatic colonized patients, contaminated environment, or both can serve as reservoirs for these pathogens, which are then spread by the hands of health care workers *(Thaver et al. 2009)*.

The increasing resistance of Gram negative bacteria to third-generation cephalosporins, is thought to be attributable to extended spectrum beta-lactamase (ESBL) production , this was observed in other studies in neonates *(Altawfiq & Antony, 2007)*. The lack of culture driven antimicrobial therapy and limited consistent infection control practices are likely to be responsible for the resistance of Gram negative organisms in this study.

About 15% of Gram negative bacteria in this study were found to be resistant to imipenem which disagree with the results reported by *(Shaw et al. 2007)*, where all Gram negative isolates were sensitive, but in agreement with a study in the Philippines which reported 20% resistance to imipenem among Gram negative bacteria *(Artemio et al. 2001)*, In vitro discrepancy in testing for carbapenem activity has been demonstrated even with automated systems . This may explain these uncommon results. More work on this issue may be of important value.

Phenotypic testing of multidrug resistance among the isolated bacteria was carried out , with results showing that, prevalence of ESBL producing gram negative bacteria was 75%, while prevalence of MRSA was 80%, prevalence of MRCoNS was 78% and prevalence of VRE was 33%. These results are in disagreement with a study carried in India (Arpita et al. 2012), which found that 14% of the isolates were ESBL producers and 29% were VRE. Methicillin resistance in S. aureus was seen in 50% of isolates and methicillin resistance noted in CoNS was 68%.

CONCLUSION

In our study we found that preterm, male neonates, who delivered vaginally with low birth weight, are more risky for developing neonatal sepsis. phenotypic testing of multidrug resistance among the isolated bacteria was carried out resulted in, Prevalence of ESBL producing gram negative bacteria was 75%, while Prevalence of MRSA 80%, Prevalence of MRCoNS 78%, and Prevalence of VRE was found to be 33%.

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الملخص العربى

أنماط مقاومه البكتيريا الممرضه للمضادات الحيويه بوحدةالعنايه المركزه للاطفال حديثى الولاده فى مستشفى سوهاج الجامعى

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الخلفيه: انتشار عدوىمجرىالدم في وحدات الرعاية الصحية الخاصه بحديثي الولادة في تزايد وماينتج عنها من قسط كبيرمن المراضة والوفيات،علاوة على أن التكلفة الاقتصادية فى تزايد مستمر كما ان مقاومة الجراثيم المسببه للمضادات الحيوية تزيد من سوء الوضع. وبالرغم من الدراسه الجيده لهذه النوعيه من العدوى في البلدان المتقدمة، الا ان الصورة ليست واضحة في البلدان النامية.

الهدف:البحث يهدف الى دراسة وبائيات الخمج الوليدى متأخر الحدوث فى وحدة العناية المركزة لحديثي الولادة من مستشفى سوهاج الجامعى، بالاضافه الى تحديد العوامل المهيئة له وكذلك البكتيريا المسببة وأنماط مقاومتها للمضادات الحيوية .

الطريقه:تضمن هذا البحث ٣٣٠ طفلا من حديثي الولادة عانوا من وجود واحد أو أكثر من علامات الخمج، تتراوح أعمارهم بين ٥ إلى ٢٨ يوما. حيث تم أخذ عينة من الدم الوريدى من كل منهم، ثم تم زرعها والتعرف على البكتريا المسببة وإجراء اختبار حساسية للمضادات الحيويه.

النتائج: كان فحص الزرع الجرثومى إيجابيا فى١١٧ (٣٦٪) من الحالات وقد وجدت نتائج العزل الايجابى اكثرحدوثا بين حديثى الولاده من الذكور(٦٦,٦٧٪) الذين ولدوا بالولاده المهبليه الطبيعيه (٦٧٪) قبل الاوان(٧٤٪) مع وزن اقل من المعدل الطبيعى (٧٥٪) ،شكلت البكتيريا سالبة الجرام نسبة (٥٦٪) من إجمالي الزرع الجرثومى، حيث كانت الكلبسيلة الرئوية هى السائده بنسبة (٢٣٪)، تليها المكورات العنقودية سالبة التخثر بنسبة (١٨٪). وكان معدل الوفيات بين الحالات ايجابية العزل الجرثومى (٤١٪). وقد كانت اغلب البكتيريا المعزوله حساسة لعقار الإميبينيم وبعضها حساسة للجيل الرابع من السيفالوسبورينات، ولكن معظم البكتيريا المعزوله ابدت مقاومة عالية لغالبية المضادات الحيوية الأخرى التي تم اختبارها، وقدأظهرت الزائفة الزنجارية أعلىمعدل للمقاومة للمضادات الحيوية، في حين أظهرت المكورات السبحيه أقل مقاومة.

الخلاصه:عوامل الخطر المحتملة لحدوث الخمج الوليدى متأخر الحدوث هى الولاده قبل الاوان وانخفاض الوزن عندالولادة وجنس الذكور. كما ان البكتيريا سالبة الجرام هى المسبب الرئيسى له،ويمكن أيضا أن نستنتج أنه يمكن استخدام الإميبينيم والسيفالوسبورينات من الجيل الرابع فى العلاج التجريبي لهذا النوع من العدوى.

التوصيات:التزام العاملين في الرعاية الصحية بالاطفال حديثى الولاده بنظافة اليدين وإجراءات الوقاية الشخصية المناسبة بجانب تطهيرالبيئة هي عوامل أساسية للحد من اكتساب العدوى المسببه للخمج الوليدى متأخرالحدوث.