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专家讲座

Prevention of respiratory syncytial viral infections in late preterm infants

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1 Introduction

The vast majority of upper and lower respiratory tract infections in children have a viral etiology. Respiratory syncytial virus (RSV) is the most common causative agent of this acute illness, principally affecting the respiratory system and varies in severity of duration. RSV is responsible for 50% -90% of hospitalizations for bronchiolitis and 25% for pneumonia. Premature infants less than 32 weeks and infants with anomalies, such as chronic respiratory insufficiency (bronchopulmonary dysplasia or chronic lung disease) and hemodynamically significant congenital heart defects, are some of the subsets of neonates particularly likely to contract RSV infections. Prophylaxis for these groups has been extensively studied and is supported by clinical guidelines in many parts of the world[1-2]. Although infants >32 weeks gestational age are less likely to have adverse health outcomes than their more premature counterparts (<32 weeks), they are still at greater risk for RSV infections than infants born at term. Available evidence suggests that late preterm infants if admitted with RSV may suffer from serious adverse clinical outcomes. The practice of RSV immunoprophylaxis appears to be different from country to country and nonexistent in many countries from third world.

The most common cause of hospitalization and rehospitalization in low and very low birth weight pre-term infants is lower respiratory tract infection, a significant part of which is due to RSV infection. The incidence of hospitalization for RSV-related lower respiratory tract infections in infants born between 33-35 weeks gestation varies from 1.8% -9.8 %[1-7]. This incidence is approximately the same as for infants with no underlying medical conditions born between 29 weeks and 33 weeks of gestation[8]. RSV hospitalization in infants of 33 to 35 weeks of gestation is associated with greater intensive care unit (ICU) and hospital length of stay, higher rates of medical complications, higher intubation rates and higher healthcare costs than infants in any other gestational age group[9]. A Canadian study has also shown that RSV hospitalization in infants born between 32 and 35 weeks of gestation is associated with an increased risk for morbidity and mortality and increased health care resource utilization[10].

In a prospective study of over 1500 infants admitted to Canadian Children's Hospitals with RSV-related lower respiratory tract infection, infants between 33-36 weeks of gestation and without other risk factors, comprised 12.9% of this cohort[11-12]. When compared to infants born at term, those born between 33 and 36 weeks of gestational age at the onset of the RSV infection had a significantly higher incidence of apnea, an increased requirement for supplemental oxygen, intensive care management and mechanical ventilation support, and consequently longer duration of hospitalization.

2 Review of available studies on late preterm infants

In this paper we will discuss the current recommendations for RSV prophylaxis using the humanized monoclonal antibody product (palivizumab, SYNAGIS®), and review two more recent studies, which analyzed the risk factors associated with hospitalization for infants be-

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tween 33 – 35 weeks gestation with RSV disease.

Prophylaxis with palivizumab for this age group has not been widely recommended by expert committees in Canada and the United States, despite data showing an 80% reduction in hospitalization rate in infants born between 32 – 35 weeks gestation age[1]. The 33 – 35 weeks gestation cohort comprises 3% – 5% of the annual birth cohort in Canada, and would constitute a large number of infants eligible for prophylaxis. The committees have instead proposed criteria based on the impact and risk of seriousness of the RSV illness. The Canadian Pediatric Society currently recommends that infants 33 through 35 weeks gestation receive prophylaxis only if they reside in remote northern areas of the country, because of the need for emergency medical transportation to tertiary care centers in the event of a severe RSV illness[13].

The American Academy of Pediatrics guidelines recommend limiting prophylaxis to infants with 2 or more of the following risk factors: child care attendance, school-age siblings, exposure to environmental air pollutants, congenital anomalies of the airways or severe neuromuscular disease[14]. Guidelines in Italy, Poland, Spain, Japan and some Latin American countries also recommend RSV prophylaxis for children of 33 to 35 weeks gestation based on risk factors[15-16]. The risk factors included vary from one country to another, and include: hospital discharge after birth during the RSV season, low birth weight, exposure to passive cigarette smoke, absence of breast-feeding, multiple birth, daycare attendance, crowding at home and school-age siblings.

A more recent study published by Law et al[3] in Canada also showed that infants born at 33 – 35 weeks of gestation may be at risk for severe RSV infection if certain risk factors are present. To identify the risk factors and determine the burden of illness, this multi-center study prospectively followed a cohort of infants born between 33 and 35 completed weeks gestation through two RSV seasons, 2000 – 2001 and 2001 – 2002. Baseline data were collected by face-to-face interviews with parents and review of medical records. The incidence of respiratory tract illnesses was monitored and cases were followed by monthly telephone calls to parents until the end of the relevant RSV season. The medical records were reviewed for emergency room visits and hospitalizations. The study enrolled 1860 subjects, of which 1832 (98.5%) were evaluated.

Of the infants followed through two RSV seasons, 140 (7.9%) infants were hospitalized for various respiratory tract illnesses, and 66 (3.8%) infants had proven RSV infection confirmed by laboratory testing[3]. The risk factors for RSV hospitalization were determined by stepwise logistic regression analyses. The independent predictors for RSV hospitalization were: (1) subject attending daycare (*OR* 12.32, 95% *CI* 2.56 – 59.34), (2) November through January births (*OR* 4.88, 95% *CI* 2.57 – 9.29), (3) preschool age siblings (*OR* 2.76, 95% *CI* 1.51 – 5.03), (4) birth weight < 10th percentile (*OR* 2.19, 95% *CI* 1.14 – 4.22), (5) male gender (*OR* 1.91, 95% *CI* 1.10 – 3.31), (6) two or more smokers in the dwelling (*OR* 1.71, 95% *CI* 0.97 – 3.00), and (7) the number of people in the household > 5 including subjects (*OR* 1.69, 95% *CI* 0.93 – 3.10) (Table 1). Interestingly, a family history of eczema appeared to be protective (*OR* 0.42, 95% *CI* 0.18 – 0.996). The authors of this study concluded that these specific host and environmental factors can be used to identify the 33 – 35 weeks gestational age infants who are at greater risk for RSV-related hospitalization, and thus may benefit from palivizumab prophylaxis[3].

A case-control study was conducted by Figueras-Aloy et al[17]. In Spain to identify the risk factors associated with RSV-related hospitalization of premature infants born at 33-35 weeks gestation. This study was conducted during the RSV season of October 2002 to April 2003. The authors prospectively followed 186 children hospitalized with RSV-infection (the cases) and 371 age-matched controls in 50 participating Spanish health institutions. Among the cases, 20.5% were admitted to the ICU, 7.6% required mechanical ventilation and no deaths were reported. Logistic regression analyses adjusted for medical center demonstrated that the risk factors associated with RSV-related respiratory infection requiring hospitalization in pre-term infants of 33-35 weeks gestation in Spain included: (1) the absolute chronological age at the start of the RSV season, i. e., born between July 15 and December 15 (*OR* 3.95, 95% *CI* 2.65 – 5.90); (2) breast feeding for 2 months or less (*OR* 3.26, 95% *CI* 1.96 – 5.42); (3) presence of one or more school-age siblings (*OR*

2.85, 95% *CI* 1.88 – 4.33); (4) 4 or more residents and visitors at home, excluding the school-age siblings and the subject (*OR* 1.90, 95% *CI* 1.19 – 3.07); and (5) a family history of wheezing (*OR* 1.9, 95% *CI* 1.19 – 3.01) (Table 2). They concluded that for premature infants born between 33 – 35 weeks gestation in Spain, these risk factors can be used to identify those who are at increased risk of RSV-related hospitalization.

Both these studies have inherent limitations. In the Canadian study, several of the risk factors identified were also found in more premature infants, not unique to the infants at 33 – 35 weeks gestation. The parents of the studied cohort tended to be better educated and reported higher household incomes than the Canadian average. At least 44 infants hospitalized for respiratory tract infection were never tested for RSV, and only those 66 cases with a positive laboratory test for RSV were used in the analysis. It is possible that if all infants were tested, an additional 20 or more cases of RSV might have been identified, strengthening the study. This small sample may have limited the statistical power to detect additional significant risk factors. The Spanish study used a case-control study design, where it is difficult to ensure consistent medical practices across participating sites and to find an appropriate control group. While these may have potentially introduced bias, the authors took steps to minimize these. In both studies, the observed RSV hospitalization rates and morbidity were similar, and comparable to other publications.

Based on the Canadian study, the investigators have pursued the development of a predictive scoring tool to assist clinical decision-making in determining the infants at greatest risk of RSV hospitalization, and who may benefit the most from RSV prophylaxis. Each one of the variables in the final logistic model was classified as present or absent using a dichotomous scale. Details on the methodology employed for the development of this tool are the subject of a separate publication, currently under review.

Table 1 Predictors for RSV hospitalization identified in the Canadian study[3]

Risk factor	*OR* (95% *CI*)	*P* value
Subject attending day-care	12.32 (2.56 – 59.34)	0.002
November through January births	4.89 (2.57 – 9.29)	<0.001
Preschool age siblings	2.76 (1.51 – 5.03)	0.001
Birth weight < 10th percentile	2.19 (1.14 – 4.22)	0.002
Male gender	1.91 (1.10 – 3.31)	0.020
Two or more smokers in the dwelling	1.71 (0.97 – 3.00)	0.064
Number of people in the household >5 including subjects	1.69 (0.93 – 3.10)	0.088
Family history of eczema	0.42 (0.18 – 0.996)	0.049

Table 2 Risk factors for RSV hospitalization identified in the Spanish study[17]

Risk factor	*OR* (95% *CI*)	*P* value
Born between July 15 and December 15, 2002	3.95 (2.65 – 5.90)	<0.001
Breast feeding for 2 months or less in total	3.26 (1.96 – 5.42)	<0.001
Presence of one or more school-age sibling	2.85 (1.88 – 4.33)	<0.001
4 or more residents and visitors at home	1.91 (1.19 – 3.07)	0.007
Family history of wheezing	1.90 (1.19 – 3.01)	0.007

* Medical Center is the Stratum Variable

3 Discussion

The treatment of infants with RSV infections has always been directed to relieving symptoms. In 1986, the United States approved Ribavirin, the only antiviral drug indicated for the treatment of RSV infection. However, its use has been controversial as its efficacy is not only clinically questionable, but it is also difficult to administer. Additionally, Ribavirin may be mu-

tagenic, and has also been referred to as teratogenic. Its use has been very limited, if not discontinued. Many unsuccessful attempts have also been made to develop a vaccine against RSV. However, this did not bear fruit as of yet. Not only did developed vaccines not prevent RSV infection, but vaccinated infants were more likely to be inflicted with even more severe disease during the next infection.

The most successful strategy for the prevention of RSV infection has been the use of passive immunization. The first specific hyper-immune gamma-globulin developed was RSV-IGIV (RESPIGAM™), which contained polyclonal antibodies obtained from human plasma, and which required intravenous administration and close monitoring. This product was found to be safe, and was also found to reduce the number of RSV-related hospitalization in infants by 41%[7]. However, the usefulness of RESPIGAM™ was limited due to the fact that its administration required an intravenous infusion over 2 – 3 hours in an out- or in-patient setting, along with careful monitoring. Since the antibodies of RESPIGAM™ are of human origin, they interfered with the live vaccine (MMR) routinely administered at 12 months of age in Canada. In addition, the volume of administration was potentially harmful to a child with cardiac, lung or renal disease who required fluid restriction. As a result of these limitations, RESPIGAM™ is no longer available in Canada.

A humanized monoclonal antibody against RSV, palivizumab (SYNAGIS®) has been available around the globe since 1998. SYNAGIS® is the only preventive treatment against RSV currently available in Canada. Since it is not derived from human plasma, it does not present any risk for the transmission of infectious agents, nor does it interfere with routine MMR or varicella vaccination. To date, a large number of infants in Canada with risk factors for severe RSV infection have received prophylactic treatment with SYNAGIS®. The ongoing monitoring of these infants has revealed very few side effects from its administration.

3.1 RSV infection in NICU

During a period of 30 years in NICU at Royal University hospital three episodes of RSV infections have occurred. All these infections were on late pre term infants between 33 to 35 weeks gestational age. Typically the presentation was with temperature instability, episodes of periodic breathing and apneas particularly strings of apneas with increasing intensity, cough, desaturation, oxygen dependency, chest X-ray findings of pneumonitis with a positive history of visitation from family with cold. In situations like this immediate response with isolation, confirmation of diagnosis with nasopharyngeal wash and cohorting of exposed infants with contact precautions are mandatory to prevent the occurrence of epidemics in the nursery. The apneas and desaturation can be severe needing high flow (1 to 3 liters of air oxygen mix), CPAP or mechanical ventilation.

With respect to preventing RSV-related hospitalizations in infants born between 33 – 35 weeks gestation, there are currently no published Canadian guidelines (or recommendations) for the use of palivizumab in this population based on host/environmental risk factors. The two publications reviewed in this paper provide evidence that certain risk factors are associated with an increased likelihood for RSV-related hospitalizations in this subset of premature infants, possibly to a level comparable to other very low birth weight infants and children with cardiac and pulmonary anomalies for which palivizumab prophylaxis is currently provided in Canada.

3.2 Use and cost of palivizumab

In Canada infants born between 33 – 35 weeks gestation during November and January are screened using a validated risk scoring tool (point system)[18]. Over the last year, the Canadian Blood Services (CBS) have approved requests of palivizumab more regularly for these 33 – 35 weeks gestational-aged infants under the 'other' category on the CBS reimbursement form, providing the treating physician supplies a letter justifying the request. At present, the CBS is prepared to modify their pre-approval reimbursement form to include specific risk factors for these infants, following publication of expert RSV prophylaxis guidelines specifying these recommendations. Therefore, it would be helpful for clinicians if expert pediatric and infectious disease committees would update the RSV prophylaxis guidelines for infants in the 33 – 35 weeks gestational age category to include the recent evidence now available on these infants. This would help provide the impe-

tus for better utilization of resources. Currently in Canada, different provinces (notably, Quebec and British Columbia) have already adopted specialized RSV prophylaxis strategies based on risk factors to protect these infants, and other jurisdictions in Canada are also starting to develop their own particular policies for the 33 – 35 weeks gestational age group (Calgary for instance). A uniform approach is therefore necessary to ensure consistent and equitable clinical practice across Canada, which would help to reduce RSV-related hospitalization in this unique and vulnerable population, particularly as we enter into another RSV season in Canada. Most European countries follow American Academy of Pediatrics guidelines for RSV prophylaxis. The mean cost of Palivizumab per child in Italy is approximately 6300 Euros. In Canada the average cost per child per season is estimated to be 7500 dollars. Many clinics pool vials and cohort infants in an attempt to reduce the high cost. To our knowledge palivizumab is not available in mainland China, however it is available in Honkong.

4 Summary

RSV prophylaxis is not routine in infant born 33 to 35 weeks gestation. Risk scoring tool can be utilized to identify infants that have significant chance for hospitalization. Premature birth is a leading cause of infant mortality and chronic pulmonary morbidity, therefore prevention of RSV hospitalization through immune prophylaxis in late preterm infants appears attractive.

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附中文参考译文(晚期早产儿呼吸道合胞病毒感染的预防)

1 引言

绝大部分儿童上呼吸道和下呼吸道感染病原体为病毒。呼吸道合胞病毒(RSV)是这类急性疾病最常见的病原体,主要影响呼吸系统,且病程各异。50% ~90% 的细支气管炎住院病例和25% 的肺炎住院病例均由 RSV 所致。在新生儿中,小于 32 周的早产儿和有慢性呼吸功能不全(支气管肺发育不良或慢性肺疾病)或有明显血流动力学异常的先天性心脏缺陷等异常的孩子特别容易感染 RSV。已经对这些群体的预防工作进行了广泛的研究,并在全世界许多地方得到了临床指南的支持。虽然胎龄大于 32 周的早产儿较小于 32 周的早产儿出现不良预后的可能性较小,但仍比足月儿更容易感染 RSV。现有证据表明,感染 RSV 住院的晚期早产儿可能会出现严重不良预后。RSV 的免疫预防工作各国不尽相同,且许多第三世界国家还没有开展此项工作。

低和极低出生体重早产儿住院和再次住院最常见的原因是下呼吸道感染,大多是由于 RSV 感染。在胎龄 33 ~35 周的婴儿中,因 RSV 下呼吸道感染而住院治疗的发生率为 1.8% ~9.8%,这一比例与胎龄 29 ~33 周且无潜在医学问题的早产儿大致相同。因 RSV 住院治疗时,胎龄 33 ~35 周的婴儿比其他任何胎龄组的婴儿需要更长的重症监护病房(ICU)和医院治疗时间,更容易出现并发症,更需要气管插管,需要更高的医疗费用。加拿大的一项研究也表明,因 RSV 住院治疗时,胎龄 32 ~35 周的婴儿发病率和死亡率更高,需要使用更多的医疗资源。

对加拿大儿童医院收治的 1500 名 RSV 下呼吸道感染婴儿进行的一项前瞻性研究中,胎龄 33 ~36 周且无其他危险因素的婴儿占了这一人群的 12.9%。与足月出生的婴儿相比,胎龄 33 ~36 周且发生 RSV 感染的婴儿出现呼吸暂停的几率明显较高,更需要输氧、重症监护和机械通气支持,因此住院治疗时间更长。

2 晚期早产儿 RSV 感染研究回顾

本文将讨论当前 RSV 预防工作中对人源化单克隆抗体产品(帕利珠单抗,SYNAGIS®)的推荐使用,并回顾两项最近的研究,这两项研究分析了与胎龄 33 ~35 周且患有 RSV 疾病的婴儿住院治疗相关的风险因素。

尽管数据显示应用帕利珠单抗可使胎龄 32 ~35 周的婴儿因 RSV 感染的住院率降低 80%,但加拿大和美国的专家委员会并没有广泛推荐对这一年龄组使用帕利珠单抗进行预防。胎龄 33 ~35 周的婴儿占加拿大年出生婴儿总数的 3% ~5%,因此有大量婴儿符合预防条件。而加拿大专家委员会根据 RSV 疾病的影响和风险提出了相关标准。目前,加拿大儿科协会建议,对于胎龄 33 ~35 周的婴儿,只有当他们居住在国内偏远的北方地区时才需要接受预防,因为出现严重 RSV 疾病时,需要紧急医疗输送至三级医疗中心。

美国儿科学会的指南建议仅对具有下列 2 项或更多风险因素的婴儿进行预防:上托儿所、有学龄期同胞、接触环境空气污染物、气道先天性畸形或严重神经肌肉疾病 。意大利、波兰、西班牙、日本和一些拉美国家的防治指南也建议根据风险因素对胎龄 33 ~35 周的婴儿进行 RSV 预防。各国防治指南中提到的风险因素不尽相同,包括:在 RSV 流行季节出生后出院、低出生体重、被动吸烟、无母乳喂养、多胎、日托、家中拥挤和有学龄期同胞。

Law 等人在加拿大发表的一项最新研究也表明,如果胎龄 33 ~35 周的婴儿存在某些风险因素,可能会出现严重 RSV 感染。为了识别这些风险因素并确定疾病负担,这项多中心研究前瞻性地对一组胎龄 33 ~35 周的婴儿跟踪调查了两个 RSV 流行季节(2000 ~2001 年和 2001 ~2002 年)。通过与其父母面谈和病历回顾收集了基线数据,每月给其父母打电话监测呼吸道疾病的发生率并跟踪病例,直到相应的 RSV 流行季节结束,同时回顾了急诊室就诊和住院治疗的病历。这项研究入组了 1860 名受试者,其中 1832 名(98.5%)得到了评估。

在跟踪了两个 RSV 流行季节的婴儿中,140 名(7.9%)婴儿因各种呼吸道疾病住院治疗,66 名(3.8%)婴儿经实验室测试证实有 RSV 感染。通过逐步逻辑回归分析确定了 RSV 住院治疗的风险因素。RSV 住院治疗的独立预测因素为:(1)日托(OR = 12.32, 95% CI = 2.56 ~59.34);(2)11 月至 1 月出生(OR = 4.88,95% CI = 2.57 ~9.29);(3)有学龄前同胞(OR = 2.76,95% CI = 1.51 ~5.03);(4)出生体重 < 第 10 个百分位(OR = 2.19,95% CI = 1.14 ~

4.22);(5)男性(*OR* = 1.91,95% *CI* = 1.10 ~ 3.31);(6)家中有两位或两位以上的吸烟者(*OR* = 1.71,95% *CI* = 0.97 ~ 3.00);(7)家庭成员人数 >5 人,包括受试者(*OR* = 1.69,95% *CI* = 0.93 ~ 3.10)(表 1)。有趣的是,湿疹家族史似乎有保护作用(*OR* = 0.42,95% *CI* = 0.18 ~ 0.996)。这项研究的作者得出的结论是,这些特定的宿主和环境因素可用于判别在胎龄 33 ~ 35 周的婴儿中哪些有较高的 RSV 住院风险,从而可能会受益于帕利珠单抗预防。

Figueras-Aloy 等人在西班牙进行了一项病例对照研究,以确定与胎龄 33 ~ 35 周的早产儿因 RSV 住院治疗相关的风险因素。这项研究在 2002 年 10 月至 2003 年 4 月的 RSV 流行季节进行。研究作者对西班牙 50 所卫生机构的 186 名住院治疗 RSV 感染的儿童(病例)和 371 名年龄匹配的对照儿童进行了前瞻性的跟踪研究。这些病例中,20.5% 在重症监护病房接受治疗,7.6% 需要机械通气,无死亡病例报告。根据医疗中心调整的逻辑回归分析表明,在西班牙胎龄 33 ~ 35 周的早产儿因 RSV 呼吸道感染住院的风险因素包括:(1)RSV 流行季节开始时的绝对实足年龄,即 7 月 15 日至 12 月 15 日出生(*OR* = 3.95,95% *CI* = 2.65 ~ 5.90);(2)母乳喂养不超过 2 个月(*OR* = 3.26,95% *CI* = 1.96 ~ 5.42);(3)有 1 个或多个学龄期同胞(*OR* = 2.85,95% *CI* = 1.88 ~ 4.33);(4)家中有 4 名或 4 名以上居住者和访客,不包括学龄期同胞和受试者(*OR* = 1.90,95% *CI* = 1.19 ~ 3.07);(5)哮喘家族史(*OR* = 1.9,95% *CI* = 1.19 ~ 3.01)(表 2)。他们的结论是,对于西班牙的胎龄 33 ~ 35 周的早产儿,这些风险因素可用来判别哪些早产儿有较高的 RSV 感染入院风险。

这两项研究都具有其内在局限性。在加拿大的研究中,有几项确定的风险因素也发现于其他早产儿中,而不仅限于胎龄 33 ~ 35 周的婴儿。研究组父母的受教育水平较高,报告的家庭收入也高于加拿大平均水平。至少有 44 名因呼吸道感染住院治疗的婴儿从未接受过 RSV 检测,分析中只包括了实验室测试 RSV 阳性的 66 例婴儿。如果所有婴儿都进行了测试,有可能会新增至少 20 个 RSV 感染病例,以增强研究效果。小样本可能限制了检测其他显著风险因素的统计功效。西班牙的研究采用病例对照研究设计,难以保证各医疗机构医疗实践的一致性,难以找到一个合适的对照组。虽然这些有可能造成了偏差,但作者采取了措施尽量减少这些偏差。在这两项研究中,观察到的 RSV 住院率和发病率与其他已发表论文的数据相似,具有可比性。

根据加拿大的研究,研究者们已致力于开发一种预测评分工具协助临床决策,确定因 RSV 入院风险最高的婴儿,他们可能从 RSV 预防中获益最多。最终逻辑模型中的每一个变量采用二分量表归类为有或无。开发这种工具所采用的方法细节是另一研究论文的主题,目前正在评审中。

3 讨论

婴儿 RSV 感染的治疗总是针对减轻症状。1986 年,美国批准了利巴韦林,这是适用于治疗 RSV 感染的唯一抗病毒药物。然而,它的使用一直具有争议,因为其功效不仅在临床上值得商榷,而且很难给药。此外,利巴韦林可能具有致突变性,也称为致畸性。即便没有停用,它的应用也十分有限。为研发抗 RSV 疫苗,也进行了许多尝试,但仍未取得成效。研发出的疫苗不但不能预防 RSV 感染,而且接种疫苗的婴儿在下一次感染中容易罹患更严重的疾病。

预防 RSV 感染最成功的策略是采用被动免疫。研发出的第一个特异性超免疫 γ-球蛋白是 RSV-IGIV(RESPIGAMTM),它含有从人血浆中获取的多克隆抗体,并需要静脉给药和密切监测。经证实,这种产品是安全的,而且可将婴儿因 RSV 住院病例数减少 41%。然而,RESPIGAMTM 的用处是有限的,因为给药需要在门诊或住院病房静脉滴注 2 ~ 3 小时,并需要密切监测。由于 RESPIGAMTM 的抗体具有人源性,它们会干扰 12 个月时在加拿大常规给予的活疫苗(麻腮风疫苗)。此外,用药剂量也可能对患有心脏、肺或肾脏疾病需要液量限制的儿童造成损害。由于这些限制,RESPIGAMTM 在加拿大不再使用。

自 1998 年以来,世界各地都出现了抗 RSV 人源化单克隆抗体帕利珠单抗(SYNAGIS®)。SYNAGIS®目前在加拿大是预防 RSV 的唯一手段。由于它不是来源于人血浆,所以不会出现任何传播传染性病原体的风险,也不干扰常规 MMR 或水痘疫苗接种。至目前为止,加拿大很多具有严重 RSV 感染风险因素的婴儿都接受了 SYNAGIS®的预防性治疗。这些婴儿的持续监测结果已说明 SYNAGIS®的副作用很少。

3.1 新生儿重症监护病房中的 RSV 感染

皇家大学医院新生儿重症监护病房在 30 年间发生了三起 RSV 感染事件,都见于胎龄 33 ~ 35 周的晚期早产儿。通常情况下,患者表现为体温不稳

定、周期性呼吸和呼吸暂停发作(尤其是强度增加的一连串呼吸暂停)、咳嗽、氧饱和度下降、氧依赖,胸部 X 光片显示肺炎并被患有感冒的家人探视。在这样的情况下,必须立即隔离,鼻咽洗液明确诊断,集中暴露的婴儿采取接触预防措施,以防止护理单元中的流行。严重呼吸暂停和氧饱和度降低的患儿可能会需要高流量通气(1 ~3 升空氧混合气)、持续气道正压通气或机械通气。

关于预防胎龄 33 ~35 周的婴儿因 RSV 入院,目前加拿大还没有已发表的指南或建议来根据宿主/环境风险因素指导这一人群使用帕利珠单抗。本文回顾的这两项研究表明,某些风险因素与此胎龄早产儿因 RSV 入院的风险增加相关,可能达到与其他极低出生体重婴儿和心肺异常的婴儿相当的水平,所以目前加拿大已提供帕利珠单抗预防。

3.2 帕利珠单抗的使用和医疗费用

在加拿大,对出生于 11 月至 1 月期间胎龄 33 ~35 周的婴儿采用经过验证的 RSV 风险评分工具进行评估,筛选出需使用帕利珠单抗的婴儿[18]。在过去的一年中,加拿大血液服务中心(CBS)已批准了胎龄 33 ~35 周的婴儿定期使用帕利珠单抗的请求,将其列在 CBS 报销申请表的“其他”类别中,条件是治疗医师应提供申请使用此药的证明信。目前,CBS 正准备修改其预先批准的报销申请表,包括这些婴儿的具体风险因素,列在说明这些建议的 RSV 专家预防指南之后。因此,如果儿科和感染性疾病专家委员会对胎龄 33 ~35 周的婴儿的 RSV 预防指南进行更新,纳入最新文献证据,这将对临床医生有所帮助,也有助于为更好地利用资源提供推动力。目前在加拿大,不同的省份(尤其是魁北克省和不列颠哥伦比亚省)已经根据风险因素采取专门的 RSV 预防策略保护这些婴儿,加拿大的其他行政辖区(例如卡尔加里)也开始为胎龄 33 ~35 周的婴儿制定专门的政策。因此,加拿大有必要采用统一的方法,以保证临床实践的一致性和公平性,这将有助于减少这一独特易感人群因 RSV 入院的风险,尤其是我们正进入加拿大另一个 RSV 流行季节。大多数欧洲国家仿效美国儿科学会的 RSV 预防指南,在意大利,每位儿童的帕利珠单抗费用平均约为 6300 欧元。在加拿大,每位儿童每个流行季节的平均费用估计为 7500 美元。许多诊所集中药物和婴儿,试图降低高费用。据我们所知,中国大陆没有帕利珠单抗,但香港有。

4 总结

RSV 感染的预防对于胎龄 33 ~35 周的婴儿不是常规。风险评分工具可用来识别 RSV 高住院几率的婴儿。早产是婴儿死亡和慢性肺疾病的主要原因,因此,通过对晚期早产儿进行免疫预防来防止因 RSV 感染入院看起来是有吸引力的。

(本文编辑:邓芳明)