·标准与讨论·

呼吸机相关性肺炎预防、诊断和治疗指南(2013)

中华医学会重症医学分会

呼吸机相关性肺炎(Ventilator-associated pneumonia, VAP)是重症医学科(ICU)内接受机械通气患者最常见的感染性疾病之一。VAP 可导致接受机械通气患者的住院时间和 ICU 留治时间延长,抗菌药物使用增加,并导致重症患者的病死率增加,严重影响重症患者的预后。随着我国重症医学的发展,机械通气技术在 ICU 应用的日益普及,如何正确诊断、有效预防与治疗 VAP 成为重症医学领域最关注的问题之一。中华医学会重症医学分会结合近年来国内外在该领域里的热点问题和研究成果,组织了专家进行讨论,应用循证医学的方法,制定了本指南,旨在对我国 ICU 内接受机械通气患者在 VAP 的诊断、预防和治疗方面的管理达成共识。

定义与流行病学

VAP 指气管插管或气管切开患者在接受机械通气 48 h 后发生的肺炎。撤机、拔管 48 h 内出现的肺炎,仍属 VAP[1-2]。

目前 VAP 在国内外的发病率、病死率均较高,导致 ICU 留治时间与机械通气时间延长,住院费用增加。国外报道,VAP 发病率为 6~52% 或 1.6~52.7/1000 机械通气日,病死率为 14%~50%,若病原菌是多重耐药菌或泛耐药菌,病死率可达 76%,归因死亡率为 20~30%[3-9]。在我国,VAP 发病率在 4.7~55.8% 或 8.4~49.3/1000 机械通气日,病死率为 19.4~51.6%[10-12]。VAP 导致机械通气时间延长 5.4~14.5 d,ICU 留治时间延长 6.1~17.6d,住院时间延长 11~12.5 d[3,13-16]。在美国,VAP 导致住院费用增加超过 4,000 美元/每次住院[16-17]。

重症患者存在多种与 VAP 发生相关的危险因素,包括与患者的基础状态、诊疗相关操作及药物治疗相关的因素等[1,3,7,10,18]。

基于其发病时间,可将 VAP 分为早发 VAP 和晚发 VAP。早发 VAP 发生在机械通气≤4 d,主要由对大部分抗菌药物敏感的病原菌(如甲氧西林敏感的金黄色葡萄球菌、肺炎链球菌等)引起;晚发 VAP 发生在机械通气≥5 d,主要由多重耐药菌或泛耐药菌(如铜绿假单胞菌、鲍曼不动杆菌、甲氧西林耐药的金黄色葡萄球菌)引起[3,9]。在我国,VAP 的致病菌多为铜绿假单胞菌和鲍曼不动杆菌 10,12,19,而部分的早发 VAP,也可由多重耐药的病原菌(如铜绿假单胞菌或甲氧西林耐药的金黄色葡萄球菌引起[20-21]。

诊 断

VAP 的诊断困难,争议较大。临床表现和影像学的改变均缺乏特异性。组织培养认为是肺炎诊断的“金标准”。因其是有创检查,临床取材存在困难,早期不常进行,不利于早期初始的经验用药。文献报道的多种检测方法目前尚无统一标准,因此各种病原学检测方法对诊断的准确性因此受到质疑。

根据现有的研究证据,VAP 的诊断主要依据临床表现、影像学改变和病原学诊断。近年来,一些与感染相关的生物标志物可提高临床对感染的识别,其对 VAP 的诊断意义值得关注。而临床肺部感染评分可行性好,能对 VAP 的诊断量化,有助于临床诊断 VAP。

一、临床诊断[22]

1. 胸部 X 线影像可见新发生的或进展性的浸润阴影是 VAP 的常见表现。

2. 如同时满足下列至少 2 项可考虑 VAP 的诊断:

(1)体温 >38℃ 或 <36℃;(2)外周血白细胞计数 $>10\times10^9$/L 或 $<4\times10^9$/L;(3)气管支气管内出现脓性分泌物;需除外肺水肿、ADRS、肺结核、肺栓塞等疾病。

二、微生物学诊断

1. 标本的留取:VAP 的临床表现缺乏特异性,早期获得病原学检查结果对 VAP 的诊断和治疗具有重要意义。疑诊 VAP 患者经验性使用抗菌药物前应留取标本行病原学检查。

获取病原学标本的方法分为非侵入性和侵入性,非侵入性方法一般指经气管导管内吸引(Endotracheal Aspiration, ETA)分泌物;侵入性方法常包括经气管镜保护性毛刷(Protected Specimen Brush, PSB)和经气管镜支气管肺泡灌洗(Bronchoalceolar Lavage, BAL)获取样本。用上述方法获取的标本进行定量培养有助于病原微生物的诊断,因此建议有条件的单位应开展细菌的定量培养。ETA 法留取标本的优点是取样快、操作简单且费用低,在临床上较易实施;缺点是容易被上气道定植菌污染。ETA 常以定量培养分离细菌菌落计数≥10^5 CFU/mL 为阳性阈值。不同的研究报告该方法敏感性和特异性变化较大,敏感性 38%~100%,特异性 14%~100%。因此该方法主要用于指导开始抗菌药物的目标治疗的药物选择及治疗过程中对病原学的动态监测。

PSB 以定量培养分离细菌菌落计数≥10^3 CFU/mL 为阳

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性阈值,其敏感性为 50%(38% ~62%),特异性为 90%(79% ~97%);BAL 以定量培养分离细菌菌落计数≥10^4 CFU/mL 为阳性阈值,其敏感性为 65%(54% ~74%),特异性为 82%(71% ~91%)[23-28]。

目前的研究表明[29-33],与 ETA 相比,通过 PSB 和 BAL 留取标本作定量培养是更准确的病原学诊断方法,但与上述有创检查方法相比,ETA 留取标本的操作简单,费用低廉,更容易实施。

推荐:与 ETA 相比,PSB 和 BAL 取气道分泌物用于诊断 VAP 准确性更高(1B)

2. 气道分泌物涂片检查:气道分泌物定量培养需要 48 ~72 h,耗时较长,不利于 VAP 的早期诊断与指导初始抗菌药物的选择。分泌物涂片检查(革兰染色法)则是一种快速的检测方法,可在接诊病人的第一时间初步区分革兰阳性菌、革兰阴性菌和真菌。研究表明,以≥2% 的白细胞内有微生物吞噬为阳性标准。分泌物涂片具有较高的敏感性和特异性(敏感性 80%,特异性 82%)[34-35]。O'Horo JC 等[36]对 24 项相关研究进行 Meta 分析发现,对发病率在 20% ~30% 的 VAP,与分泌物培养相比,分泌物涂片对 VAP 诊断的敏感性和特异性分别为 79% 和 74%,其中阳性预测价值为 40%,阴性预测价值超过 90%。因此对疑诊 VAP 患者,分泌物涂片阳性对 VAP 微生物学诊断参考价值有限,不应作为初始经验性治疗的抗生素选择的绝对依据[36-37]。而分泌物涂片阴性,特别是革兰阳性菌的涂片结果为阴性时,对除外 VAP 更有意义。

推荐:气道分泌物涂片检查,有助于 VAP 诊断和病原微生物类型的初步判别(1C)

三、感染的生物标志物

C-反应蛋白(CRP)和前降钙素原(PCT)是近年来临床上常用的判断感染的生物学指标[38]。由于 CRP 水平在非感染性疾病中也常升高,因此对感染性疾病的诊断特异性较低。PCT 与肺部感染密切相关,其水平升高常提示机体存在细菌感染,而且随着病原微生物被清除,PCT 的水平下降[39]。研究表明,在疾病治疗过程中动态监测 PCT 的变化有助于指导抗菌药物的使用及缩短其使用周期,但由于其敏感性较低,并缺乏高质量的什么研究,目前还无证据支持 PCT 有助于 VAP 的诊断[40-41]。

对机械通气患者的前瞻性研究提示,人可溶性髓系细胞触发受体(Soluble Triggering Receptor Expressed on Myeloid Cells-1,sTREM-1)的表达水平是肺炎非常强的独立预测因素,但是否有助于 VAP 的诊断,研究结果则差异较大,甚至相反[42-44]。因此,目前 sTREM-1 尚未能在临床推广使用。

1,3-β-D 葡聚糖(BG)和半乳甘露聚糖(GM)是目前协助临床诊断侵袭性真菌感染常用的生物标志物。一项对免疫功能抑制患者的研究发现,肺泡灌洗液的 GM 对鉴别曲霉菌引起的 VAP 有较好的敏感性和特异性,但 BG 和 GM 在免疫功能正常的机械通气患者中研究甚少,能否作为 VAP 病原学鉴别的生物标志物尚需更多的证据支持[45-46]。

四、感染和定植的鉴别分析

机械通气患者如果出现感染的临床征象(如发热、黄痰、白细胞增多或减少)及肺部渗出的影像学表现,则需行微生物学检查以明确病原菌。下气道分泌物定量培养结果有助于鉴别病原菌是否为致病菌,经 ETA 分离的细菌菌落计数≥10^5 CFU/ml、经气管镜 PSB 分离的细菌菌落计数≥10^3 CFU/ml,或经 BAL 分离的细菌菌落计数≥10^4 CFU/ml 可考虑为致病菌;若细菌浓度低于微生物学诊断标准,仍需结合宿主因素、细菌种属和抗菌药物使用情况综合评估[47-49]。

五、血培养和胸腔积液的培养

血培养是诊断菌血症的"金标准",但对 VAP 诊断的敏感性一般不超过 25%,而且 ICU 患者常置入较多的导管,即使血培养阳性,细菌亦大部分来自于肺外,源自肺炎的菌血症不超过 10%[50-52]。胸腔积液的培养在 VAP 诊断中的研究尚少,若患者有胸腔感染的征象,则要进行诊断性胸腔穿刺以排除是否并发有脓胸或肺炎旁胸腔积液[53]。

六、临床肺部感染评分(CPIS)

对 VAP 的诊断进行量化有利于 VAP 诊断。1991 年 Pugin J[54]等提出了临床肺部感染评分(CPIS),该评分是综合了临床、影像学和微生物学的情况,用于诊断肺炎并评估感染的严重程度,由六项内容组成:(1)体温;(2)外周血白细胞计数;(3)气管分泌物情况;(4)氧合指数(PaO_2/FiO_2);(5)胸部 X 线片示肺部浸润进展;(6)气管吸出物微生物培养。2003 年 Luna 等[55]对 CPIS 进行了修订,去除了对痰培养结果的要求,称为简化 CPIS,利于早期评价患者肺部感染程度。

2011 年发表的评价 CPIS 在 VAP 诊断中作用的 Meta 分析,共收录了 13 篇文献,大部分以 BALF 定量培养作为诊断标准,2 篇文章与病理结果对比,1 篇文章与 PSB 定量培养结果对比,结果显示,CPIS 诊断 VAP 的敏感性为 65%(95% *CI* 61% ~69%),特异性为 64%(95% *CI* 60% ~67%),诊断 OR 值为 4.85(95% *CI* 2.42 ~9.71),AUC 为 0.748(95% *CI* 0.65 ~0.85),CPIS 在 VAP 的诊断强度属于中等[56]。但该评分系统简单易行,研究显示其可用于评估感染的严重程度,指导抗菌药物的调整时机,及时停用抗菌药物,减少不必要的暴露。因此,应用 CPIS 评分系统,可有助于对 VAP 的诊断。

推荐:CPIS 有助于诊断 VAP(1C)

预　防

VAP 是机械通气患者常见并发症,不仅延长通气时间和住院天数(时间),医疗成本增加,而且还是危重病患者重要的致死原因。目前已证实多种预防措施可降低 VAP 的发病率,故采用适当的措施以预防 VAP 对临床非常重要。

一、与器械相关的预防措施

1. 呼吸机清洁与消毒:呼吸机的消毒主要是指对呼吸机整个气路系统,如呼吸回路、传感器、内部回路及机器表面的消毒,若未按呼吸机说明书的正规程序执行,或将规定一次性使用的物品重复使用,会影响其安全性和有效性[57]。

清洁、消毒呼吸机时，应遵照卫生行政管理部门对医疗机构的消毒管理规定和呼吸机的说明书规范进行，所有一次性部件使用后应按照卫生部门相关规定丢弃并保证环境安全。

2. 呼吸回路的更换：呼吸回路污染是导致 VAP 的外源性因素之一。既往研究认为，每天更换呼吸回路可减少 VAP 的发生。近年的 RCT 研究分别比较了使用加热湿化器/热湿交换器的患者，2 d 更换和不定期更换呼吸回路（管路破损或被污染时随时更换）[58-59]，两种更换方法对 VAP 发病率无影响。还有两项 RCT 研究发现，无论呼吸回路 7 d 更换、2～3 d 更换，还是不定期更换，VAP 的发病率均无明显差别[60-61]，不定期更换呼吸回路产生的费用更少[60]。Han[62] 的 Meta 分析也发现，延长呼吸回路更换时间有降低 VAP 发病率的趋势。因此，机械通气患者无需定期更换呼吸回路，当管路破损或被污染时应及时更换。

推荐：机械通气患者无需定期更换呼吸回路（1A）

3. 湿化器类型对 VAP 发生的影响：加热湿化器（Heated Humidifiers，HHs）是以物理加热的方法为干燥气体提供适当的温度和充分的湿度，为主动湿化方式；热湿交换器（Heat and Moisture Exchangers，HMEs）是模拟人体解剖湿化系统而制造的替代性装置，它收集并利用呼出气中的热量和水分以温热和湿化吸入的气体，为被动湿化方式。对需要高流量（60～100 L/min）送气的患者或存在气道分泌物异常黏稠、黏液栓或有痰痂形成时通常选用 HHs，而 HMEs 常在运输、麻醉等短时间的通气时应用。在 VAP 的预防方面，两种湿化方式的孰优孰劣仍存争议。早期研究表明，HMEs 较 HHs 可降低 VAP 的发病率[63-65]。随着含加热导丝的 HHs 在临床的应用，近年来的研究认为，两种湿化方式对 VAP 的发病无明显影响[66-67]，甚至使用 HHs 的 VAP 发病率会更低[68]。多篇 Meta 分析显示，应用 HMEs 与 HHs 间 VAP 的发病率差异无统计学意义[69-72]，且对患者的总体病死率、ICU 留治时间、机械通气时间及气道阻塞发生率亦无影响[69]。亚组分析显示，与不含加热导丝的 HHs 相比，HMEs 组 VAP 的发病率更低[72]。目前研究表明，机械通气患者无论采用热湿交换器还是含加热导丝的加热湿化器作为湿化装置，均不影响 VAP 的发生[73-80]，但具体选用何种湿化装置尚需结合各自的适应证和禁忌证综合考虑。

建议：机械通气患者可采用热湿交换器或含加热导丝的加热湿化器作为湿化装置（2B）

4. 热湿交换器的更换：热湿交换器因能节约费用、保持管路干洁和减少护理工作量等优点广泛应用于临床。多数产品说明书建议每天更换 1 次[81]。但 2 项 RCT 研究显示，每 5 天或 7 天更换热湿交换器（HMEs）与每天更换相比，两者在 VAP 发病率、气道细菌定植及对气道阻力的影响方面差异均无统计学意义，而频繁更换湿化器明显增加费用[81-82]。

推荐：机械通气患者若使用热湿交换器，每 5～7 天更换一次，当热湿交换器受污、气道阻力增加时应及时更换（1B）

5. 细菌过滤器：细菌过滤器常放置在吸气管路和（或）呼气管路端。放置在吸气管路端可防止呼吸机送出气体内的病原体进入患者气道，放置在呼气管路端可防止患者呼出气中所含病原体污染呼吸机，细菌过滤器使用的缺点是可增加气道阻力和无效腔。已有 RCT 研究显示[83-84]，在呼吸机的吸气管路和呼气管路端均放置细菌过滤器，并未降低 VAP 的发病率，也不能缩短患者 ICU 留治时间和机械通气时间。对怀疑（疑似）或确诊为肺结核的机械通气患者，应在呼气管路端放置细菌过滤器，避免污染呼吸机和周围环境[85]。

建议：机械通气患者不常规使用细菌过滤器（2C）

6. 吸痰装置及更换频率：吸痰是机械通气患者最常进行的侵入性操作之一，对清除气道分泌物、维持气道通畅、改善氧合具有重要意义[86]。以往多采用开放式吸痰装置，但由于在操作过程中需要分离患者与呼吸机间的管道连接，不利于保持气道压力和密闭性。上世纪 80 年代后期引入了密闭式吸痰装置[87]，因其不影响患者与呼吸机管路的连接，可维持呼气末正压和减少对周围环境的污染[86]，临床上应用日渐增多。但多篇 Meta 分析提示，密闭式吸痰装置和开放式吸痰装置在机械通气患者的 VAP 发病率、病死率及 ICU 留治时间方面均无明显差异[86,88-89]。目前研究表明，采用开放或密闭式吸痰装置均不影响 VAP 的发生[90-99]。

对于使用密闭式吸痰装置时的更换频率，2 项 RCT 研究表明，与 24 h 更换相比，48 h 更换甚至不更换对 VAP 的发病率无影响[100-101]，两组在住院病死率、住院时间方面也无差异，而不更换组则明显节约医疗费用[100]。

推荐：除非破损或污染，机械通气患者的密闭式吸痰装置无须每日更换（1B）

7. 纤维支气管镜：在 ICU 内，纤维支气管镜（简称纤支镜）的应用常包括纤支镜引导下气管插管、纤支镜诊断（分泌物取样、活检）和经纤支镜气道分泌物引流等。2 个观察性研究显示，ICU 的纤支镜操作是 VAP 发生的独立危险因素[102-103]。采用细菌分子流行病学调查的方法对纤支镜和患者分泌物培养出的铜绿假单胞菌进行同源性分析显示来源一致，说明纤支镜在患者间的细菌传播中有重要作用[104]。提醒我们严格管理内镜的消毒、灭菌和维护具有重要的临床意义。

二、与操作相关的预防措施

1. 气管插管路径与鼻窦炎防治：有创机械通气患者所建立的人工气道（包括气管插管和气管切开）目的是进行机械通气、清理呼吸道分泌物以及保持患者气道通畅。气管插管可通过经口途径和经鼻途径建立。虽然两种途径建立的人工气道各有不同的优缺点，包括建立的难易、管径的不同、可放置时间的差异、患者的舒适程度、对口腔及口腔护理的影响、气道阻力及气道管理特点等不同，临床可根据具体情况选择应用[105-107]。有 RCT 研究认为，尽管经口气管插管的气道并发症较经鼻气管插管多，但经口气管插管可降低鼻窦炎的发病率。气管插管患者继发鼻窦炎是 VAP 的高危因素，且缺乏临床特征。临床医生应对机械通气患者保持识别鼻窦炎的警惕，当机械通气患者出现不明原因的发热时，需

考虑是否并发鼻窦炎[108]。床旁鼻窦 X 光片检查有助于诊断,确诊则需行鼻窦 CT 检查。一项 RCT 研究比较了 2 组患者,实验组在经鼻插管后行常规 CT 检查,若存在鼻窦炎,立即开始抗菌药物治疗;对照组则不进行 CT 检查,也未予治疗鼻窦炎。最后结果提示,实验组 VAP 发病率明显低于对照组。Pneumatikos I[109]的研究中使用塞洛唑啉滴鼻液及布地奈德鼻喷预防鼻窦炎可减少影像学上的鼻窦炎的发生,但并不能减低 VAP 的发病率[109]。

推荐:经鼻气管插管可增加鼻窦炎的发病率(1B)

建议:经鼻气管插管患者出现难以解释的发热,需行影像学检查评估是否患有鼻窦炎,并及时治疗(2B)

建议:应用药物可预防鼻窦炎,但不降低 VAPg 发病率(2C)

2. 声门下分泌物引流:上气道分泌物可聚集于气管导管球囊上方,造成局部细菌繁殖,分泌物可顺气道进入肺部,导致肺部感染。因此采用声门下分泌物引流可有效预防肺部感染[110]。持续声门下吸引是采用负压吸引装置对痰池上分泌物进行持续性引流,引流充分(前后不连贯),但可出现局部黏膜干燥、出血、影响局部血供等并发症。间断声门下吸引则间断进行分泌物的引流,如患者分泌物较多时则不能保证充分引流,增加感染几率。近期 11 项 RCT[111-122]的 Meta 分析显示,持续吸引和间断吸引声门下分泌物均可明显降低 VAP 的发病率;但目前暂无研究比较持续和间断声门下吸引对 VAP 发病率的影响。

推荐:建立人工气道患者应行声门下分泌物引流(1B)

3. 气管切开的时机:长期机械通气的患者常需要行气管切开术,相对于气管插管,气管切开能减少无效腔、增加患者的舒适度、利于口腔护理和气道分泌物引流、可能有助于缩短机械通气时间等优点。但由于是有创性操作,可出现出血、皮下/纵膈气肿及气道狭窄等并发症,因此选择气管切开的时机非常重要[123-124]。目前对气管切开的时机可分为早期和晚期,多项 RCT 研究界定早期气管切开为机械通气 8 d 以内,晚期气管切开为机械通气 13 d 以上[123-129]。多项 RCT 研究的 Meta 分析提示,与晚期气管切开相比,早期行气管切开不降低已建立人工气道的患者 VAP 的发病率,且两者对早期病死率的影响无明显差别[123-129]。

建议:机械通气患者早期气管切开不影响 VAP 的发病率(2B)

4. 动力床治疗:机械通气患者需保持相对静止的半坐卧位,可引起黏膜纤毛运输能力下降、肺不张及肺静脉血流改变[130],因此临床上可用人工为机械通气患者翻身或动力床治疗以改变患者体位,减少并发症。动力床治疗(kinetic bed therapy)是对机械通气的重症患者使用可持续旋转及保持至少 50°以上翻转的护理床,减少患者因长期卧床而出现的并发症。通常包括连续横向旋转治疗、振动治疗和连续姿势的振荡等方法[131-138]。目前关于动力床在重症患者使用方面的研究并未考虑患者对此项治疗的耐受力,因此研究结果具有一定的局限性。多项 RCT 研究[130-141]的 Meta 分析显示,与人工为机械通气患者翻身相比,动力床治疗可以降低 VAP 的发病率,但尚无证据提示其能够降低 ICU 病死率,缩短机械通气时间及 ICU 留治时间,且费用、安全性和可行性等缺陷限制了其应用。

建议:机械通气患者应用动力床治疗可降低 VAP 的发病率(2B)

5. 抬高床头使患者保持半坐卧位:半坐卧位最初只用于行肠内营养的患者,Drakulovic[142]于 1999 年提出半坐卧位在 VAP 的预防方面亦有重要作用,美国胸科协会、加拿大重症监护试验中心及疾病控制与预防中心均推荐抬高床头(30°-45°)可有效预防 VAP,尤其利于行肠内营养的患者,可减少胃内容物反流导致的误吸;但抬高床头 45°不仅患者难以耐受,且增加护理难度[143]。Drakulovic MB[142]的 RCT 研究结果显示,抬高床头 45°(实验组 39 人)与平卧位 0°(对照组 47 人)相比,抬高床头的患者 VAP 的发病率较对照者有所下降(RR = 0.23;95% CI 0.07 ~ 0.72)。Keeley L[144]的 RCT 研究结果显示,抬高床头 45°(实验组 17 人)与 25°(对照组 7 人)相比,患者 VAP 的发病率无明显差异(RR = 0.55;95% CI 0.22 ~ 1.33)。由于上述 2 项研究均为小样本研究,其结果尚存争议。近期 3 项 RCT 研究[142,144-145]的 Meta 分析结果提示,半坐卧位虽可降低 VAP 的发病率,但 van Nieuwenhoven CA[145]的研究指出多数患者无法持续耐受抬高床头至 45°(实验组患者 85% 的时间无法抬高床头至 45°)。因此,对于机械通气的患者,在保证患者可以耐受,且不影响医疗效果、不增加护理难度的条件下,抬高床头使患者保持半坐卧位可提高氧合,减少面部水肿,减少肠内营养患者出现反流和误吸。

推荐:机械通气患者应抬高床头以降低 VAP 的发病率(1C)

6. 俯卧位通气:较早的 RCT 研究指出,俯卧位通气用于急性肺损伤(ALI)和急性呼吸窘迫综合征(ARDS)患者,可在一定程度上降低 VAP 的发病率、缩短机械通气时间及 ICU 留治时间。由于这些 RCT 均为小样本研究,降低 VAP 发病率的机制不明,其结果尚存争议[146-149]。Beuret 等的研究[150]发现,对昏迷(格拉斯哥昏迷评分≤9 分)的机械通气患者行 4 h/d 的俯卧位通气不能降低 VAP 的发病率。近年 5 个 RCT 研究[1-5]的 Meta 分析结果也显示,与仰卧位相比,俯卧位通气不能降低 VAP 的发病率及病死率,其可行性与安全性也限制了其应用。

7. 肠内营养:机械通气患者常存在胃肠道革兰阴性肠杆菌的定植[151]。Altintas ND 的研究[152]提出,机械通气患者无论是肠内还是肠外营养,其 VAP 的发病率、ICU 留治时间、ICU 病死率均无明显差异,但进行肠外营养的患者其通气时间较长。2010 年的一项研究[153]提出,允许适当的胃潴留量可减少患者营养支持的中断,从而增加营养吸收及减少不良反应。亦有观察性研究[154]指出,接受胃潴留量监控的患者在营养吸收方面有优势,不良反应较少。因此,可根据患者的具体情况调节管饲的速度和量,同时行胃潴留量的监

测,可避免胃胀气,减少误吸。鼻饲方法常分为经鼻胃管、经鼻十二指肠管及经鼻空肠管等途径。有研究[155]指出,经鼻肠营养和经鼻胃内营养对机械通气患者 VAP 发病率的影响并无差异,但空肠内营养使患者吸收能量及蛋白质更多。2009 年 CW Hsu 的研究[156]提出,经十二指肠营养较胃内营养的呕吐率低,且能更早达到营养目标。5 项 RCT 研究[155-159]的 Meta 分析发现,经鼻肠营养与经鼻胃内营养相比,前者可降低 VAP 的发病率,但两者在病死率方面并无差异。

建议:机械通气患者选择经鼻肠管进行营养支持可降低 VAP 的发病率(2B)

8. 气管内导管套囊的压力:套囊是气管内导管的重要装置,可防止气道漏气,防止口咽部分泌物流入,防止胃内容物的反流误吸。置入气管内导管后应使套囊保持一定的压力,以确保其功效并减轻气管损伤[160-162]。L Bouadma [160]的回顾性研究发现,监测套囊压力,使之保持在 20 cm H_2O(1 cm H_2O = 0.098 kPa)以上可降低 VAP 的发病率(23.5/1000 机械通气日降至 14.9/1000 机械通气日,$P < 0.0001$)。J Rello [161]对机械通气患者进行每 4 小时套囊压力监测发现,与不监测相比,VAP 发病率有所降低。Nseir S[162]等的研究发现,与间断监测气管套囊压力相比,持续监测套囊压力并使目标压力控制在 25 cm H_2O,可有效降低 VAP 的发病率。

建议:机械通气患者应定期监测气管内导管的套囊压力(2C)

建议:持续控制气管内导管的套囊压力可降低谁的 VAP 的发病率(2B)

9. 控制外源性感染:引起 VAP 的病原体常可通过医护人员及环境感染患者。Larson[163]发现,21% 的医护人员手上定植有革兰阴性菌,如肺炎克雷伯菌、鲍曼不动杆菌及阴沟肠杆菌。Maki 随机抽查 ICU 医护人员的手,其中 64% 的手定植金黄色葡萄球菌[164]。疾病预防与控制中心报告推荐,医护人员进应行严格的手卫生(包括洗手及酒精消毒)。多篇回顾性研究分析结果表明,进行严格的手卫生可降低 VAP 的发病率[165-168](干预前后 VAP 下降率 53.62% ~ 69.23%,$P < 0.05$)。医护人员的教育不容忽视,将引起 VAP 的危险因素对 ICU 的医护人员进行宣教,制作教育手册发放给医护人员,以小组的形式定期进行学习和考核。多项回顾性对照研究[165-166,169-172]均表明,对医护人员进行宣教可显著降低 VAP 的发病率及缩短机械通气时间。此外,2008 年英国关于 HAP/VAP 指南亦指出,环境卫生和保护性隔离均为切断外来感染的重要途径,是院内感染控制的重要措施,在预防 VAP 的发生中非常重要[172-179]。因此,严格手卫生、对医护人员进行宣教、加强环境卫生及保护性隔离均可于一定程度上切断外源性感染途径,降低 VAP 的发病率。

推荐:加强医护人员手卫生可降低 VAP 的发病率(1C)

10. 口腔卫生:建立人工气道在一定程度上破坏了机械通气患者口鼻腔对细菌的天然屏障作用,因此对机械通气患者进行严格有效的口腔卫生护理是对气道的重要保护[180-181]。口腔卫生护理方法包括使用生理盐水、洗必泰或聚维酮碘冲洗、用牙刷刷洗牙齿和舌面等[180-197]。2 项 RCT 研究[182-183]表明,聚维酮碘与生理盐水冲洗比,虽然 2 组患者病死率无差异,但使用聚维酮碘可有效降低 VAP 的发病率。4 项 RCT 研究[184-187]的 Meta 分析发现,在普通口腔护理的基础上加用牙刷刷洗牙齿和舌面,不影响(?)VAP 发病率。多项 RCT 研究分别采用 2%、0.2% 及 0.12% 洗必泰护理口腔[181,188-197],其综合结果的 Meta 分析提示,以洗必泰护理口腔可有效降低 VAP 的发病率。

推荐:机械通气患者使用洗必泰进行口腔护理可降低 VAP 的发病率(1C)

11. 呼吸机相关性气管支气管炎(Ventilator-Associated Tracheobronchitis,VAT):目前文献报道,VAT 的发病率约为 1.4% ~10%,认为是患者肺部感染最终发展为 VAP 的重要原因。尽管 VAT 目前尚无明确统一的定义,但一般情况下可采用下述标准:不明原因的发热(>38℃);脓性分泌物;气管抽吸物或支气管镜检查标本培养结果阳性(定量或半定量);插管 48 h 后,常规 X 线胸部影像学显示无新的或进行性加重的肺浸润影[198-199]。近年来有学者认为,VAT 是肺部感染最终发展为 VAP 的重要原因。有 RCT 研究[198]提示,治疗 VAT 可有效降低 VAP 的发病率,且不增加耐药率。提示,有针对性地使用抗菌药物治疗 VAT,可能是预防 VAP 和改善患者疗效的新策略。

建议:治疗 VAT 可有效降低 VAP 的发病率(2C)

12. 早期康复治疗:康复治疗包括一般活动治疗和专业的呼吸功能康复治疗,以及电刺激等物理治疗,此外心理治疗也包含在康复治疗之内。早期康复治疗一般指机械通气 24 ~48 h 内或度过急性期后开始的康复治疗[200]。有文献报道[200-201],早期康复治疗有助于患者功能状态的恢复,防止肌肉无力和肌肉萎缩,提高患者出院时的总体机体功能状态及总体生存时间,但对患者的机械通气时间、ICU 留治时间及病死率无明显影响,尚未见研究报道康复治疗与 VAP 发病率的关系。

三、药物预防

1. 雾化吸入抗菌药物:雾化吸入抗菌药物可使呼吸道局部达到较高的药物浓度,对全身影响小,理论上可作为预防 VAP 的一项措施。但综合 2 项 RCT 研究显示[202-203],对 VAP 高危人群雾化吸入头孢他啶,并不降低 VAP 的发病率。由于研究样本量小,研究对象均为创伤患者,尚不能充分说明其对细菌耐药的影响。

建议:机械通气患者不常规使用雾化吸入抗菌药物预防 VAP(2C)

2. 静脉使用抗菌药物:尽管有 3 项 RCT 研究表明[204-206],预防性静脉应用抗菌药物可降低 VAP 的发病率,但并不降低病死率,且需要注意的是,这 3 项研究中有 2 项研究的对象是头部外伤或创伤等 VAP 高危人群,也未对细菌耐药性进行评价。故机械通气患者不应常规静脉使用抗菌药物预防 VAP,如头部外伤或创伤患者,需要应用时应考

虑细菌耐药问题。

3. 选择性消化道去污染/选择性口咽部去污染：选择性消化道去污染（selective digestive tract decontamination，SDD）是通过清除患者消化道内可能引起继发感染的潜在病原体，主要包括革兰阴性杆菌、甲氧西林敏感的金黄色葡萄球菌及酵母菌等，达到预防严重呼吸道感染或血流感染的目的[207-208]。选择性口咽去污染（selective oropharyngeal decontamination，SOD）是 SDD 的一部分，主要清除口咽部的潜在病原体。经典的 SDD 包括以下四个方面：（1）静脉使用抗菌药物，预防早发的内源性感染；（2）口咽（SOD?）和胃肠道局部应用不易吸收的抗菌药物：0.5 g PTA［P：多粘菌素 E；T：妥布霉素；A：两性霉素 B］凝胶或 2% PTA 糊涂抹口咽，每日 4 次；口服包含 100 mg 多粘菌素 E + 80 mg 妥布霉素 + 500 mg 两性霉素 B 的 10 ml 悬液，每日 4 次；预防晚发的内源性二重感染；（3）严格的卫生制度预防潜在病原体的传播，气管切开的患者局部涂抹 PTA 凝胶或 PTA 糊，补充目的；（4）每周 2 次咽喉和肠道标本的病原学监测，可评估治疗的有效性，并利于早期发现耐药菌[207]。

现有的 RCT 研究结果提示，对机械通气患者进行 SDD 或 SOD 后，虽对 ICU 病死率、院内病死率无明显影响，也不影响 ICU 留治时间、机械通气时间，但可降低 VAP 的发病率，也不增加细菌的耐药和治疗总费用[209-221]。2009 年的一项高质量 RCT 研究共纳入机械通气患者 5000 余例观察什么，结果显示，进行 SDD 或 SOD 后分别降低 VAP 病死率 3.5% 和 2.9%[209]。该研究的另一项分析表明，患者进行 SDD 或 SOD 后，呼吸道耐药菌的定植率也明显减少[222]。

建议：机械通气患者可考虑使用 SDD 或 SOD 策略预防 VAP（2B）

4. 益生菌：益生菌是指正常肠道存在的活的微生物[223]。危重患者常因肠蠕动减弱、应激性激素增加（?）、药物的影响及营养元素不足等原因，继发肠道微生物菌群的改变，表现为潜在致病菌的优势生长。益生菌可起到菌群调节作用，对胃肠道的结构和功能产生有益的影响。

对机械通气患者应用益生菌是否可降低 VAP 的发生，目前仍存争议，根据近几年的研究，近两年发表了 5 篇 Meta 分析和系统回顾（?），其中两篇文章提示危重患者应用益生菌可降低 VAP 的发病率，并可降低病死率[223-224]，而另有 2 项研究则得出相反的结果[225-226]，还有一篇文章显示[227]，创伤患者应用益生菌可显著降低 VAP 的发病率和缩短 ICU 留治时间，但对病死率无影响。分析这些研究结论相悖的原因，发现纳入标准不同是重要问题。若严格按照 VAP 的定义，现有的 RCT 研究显示，对机械通气患者应用肠道益生菌不能降低 VAP 的发病率和病死率[228-233]。

建议：机械通气患者不建议常规应用肠道益生菌预防 VAP（2B）

5. 预防应激性溃疡：一项大型队列研究显示，呼吸衰竭（机械通气 > 48 h）是消化道出血的独立危险因素[234]。综合目前的 RCT 研究显示，预防应激性溃疡并不降低机械通气患者消化道出血的风险，同时对 VAP 的发病率和病死率无影响[235-237]。但对有多种消化道出血高危因素（如凝血功能异常、头外伤、烧伤、脓毒症、使用大剂量糖皮质激素等）的机械通气患者，预防应激性溃疡可使患者明显获益[238]。

目前预防应激性溃疡的药物主要有胃黏膜保护剂（硫糖铝）和胃酸抑制剂（抗酸剂、质子泵抑制剂和 H_2 受体拮抗剂）。现有的资料表明，与 H_2 受体拮抗剂相比，机械通气患者应用硫糖铝预防应激性溃疡可降低 VAP 的发病率。但一项高质量的 RCT 研究表明[239]，相比 H_2 受体拮抗剂，应用硫糖铝会增加消化道出血风险。硫糖铝与抗酸剂比较的 RCT 研究表明[240-242]，两者在 VAP 发病率、病死率方面无差异。目前暂无硫糖铝与质子泵抑制剂对 VAP 发病影响比较的 RCT 研究。而质子泵抑制剂与 H_2 受体拮抗剂对 VAP 发病率影响的 RCT 研究显示，2 种药物无差别，但质子泵抑制剂组的消化道出血风险显著低于 H_2 受体拮抗剂组[243]。因此，预防机械通气患者的应激性溃疡，硫糖铝可降低 VAP 发生的几率，但需评估消化道出血的风险。

四、集束化方案

机械通气患者的集束化方案（ventilator care bundles，VCB）最早由美国健康促进研究所（Institute for Healthcare Improvement，IHI）提出[244]，IHI 的 VCB 主要包括以下 4 点：（1）抬高床头；（2）每日唤醒和评估能否脱机拔管；（3）预防应激性溃疡；（4）预防深静脉血栓。而 VCB 的每一点均基于改善机械通气患者预后的证据总结得出的。随着研究的深入，许多新的措施因可降低 VAP 发病率而被加入到集束化方案中，包括口腔护理、清除呼吸机管路的冷凝水、手卫生、带手套、翻身等[245-246]。尽管观察性研究表明，VCB 也可以减少 VAP 的发生，但其中只有“抬高床头”和“每日唤醒”有证据表明其直接降低 VAP 的发病率，而“预防深静脉血栓”和“预防应激性溃疡”并不直接影响 VAP 患者的结局[247]。2009 年的一篇系统综述比较了 VCB 方案对 VAP 发病率的影响[248]，其纳入了 4 项研究，结果显示在实施 VCB 前，VAP 发病率是 2.7 ~ 13.3/1000 机械通气日，实施后降至 0.0 ~ 9.3 例/1000 机械通气日[248]。目前的研究表明，对机械通气患者实施集束化方案可有效降低 VAP 的发病率，对于临床具体什么呀，在遵循循证医学原则的基础上，可根据本单位具体情况和条件，制定适合自己有效、安全并易于实施的集束化方案。

推荐：机械通气患者应实施集束化方案（1C）

治　疗

一、VAP 的抗菌药物治疗

（一）抗菌药物初始经验性治疗原则

1. 初始经验性抗感染治疗的给药时机：初始经验性治疗的定义是临床诊断为 VAP 的 24 h 内即开始抗感染治疗。此时，病原菌尚未明确，有可能因药物未能覆盖致病菌而导致治疗不当。但多项临床研究显示，如临床诊断超过 24 h 或获得微生物学检查结果后开始给药（延迟给药），即使接

受了恰当的治疗,因抗感染治疗时机延迟,仍可使 VAP 病死率升高,医疗费用增加,机械通气时间和住院天数延长[249-252]。

推荐:VAP 患者应尽早进行抗菌药物的经验性治疗(1C)

2. 初始经验性抗感染治疗抗菌药物的选择:尽管有多个评估经验性抗感染治疗 VAP 临床疗效的 RCT 研究,但至今仍无对 VAP 能取得最佳疗效的抗感染治疗方案。研究提示,在初始经验性抗感染治疗时,选择抗菌药物应重点考虑下述 3 个因素[253-262]:VAP 发生时间(早发/晚发)、本地区(甚至本病区)细菌流行病学监测资料(如病原菌谱及耐药谱等)、患者是否存在多重耐药(Multidrug -Resistant,MDR)病原菌感染高危因素(如 90 d 内曾使用抗菌药物,正在接受免疫抑制治疗或存在免疫功能障碍,住院时间 5d 以上,居住在耐药菌高发的社区或特殊医疗机构等)。

早发 VAP 和 MDR 病原菌感染低危患者,抗菌药物初始经验性治疗时无需选择广谱抗菌药物;晚发 VAP 可能由 MDR 病原菌引起,则应选择广谱抗菌药物,以确保疗效,并减少诱发耐药菌产生的机会[263-264]。VAP 可能致病菌与经验性治疗抗菌药物的选择建议见表 1。

3. 抗菌药物初始经验性治疗单药/联合用药决策:由于初始经验性抗感染治疗是医生对患者可能感染病原菌的主观判断结果,治疗选择可能存在不准确性。为克服此问题,临床医生必须收集更多病史、临床及流行病学资料以提高判断准确性。多项 RCT 研究及 Meta 分析对单药和联合用药(同时应用两种或两种以上抗菌药物)治疗 VAP 的疗效及预后进行了评估,包括美罗培南与头孢他啶联合阿米卡星的比较;头孢吡肟与头孢吡肟联合阿米卡星/左氧氟沙星的比较等。结果只提示,对铜绿假单胞菌、鲍曼不动杆菌或多重耐药菌感染,联合用药组初始经验性抗感染治疗药物选择合理率更高,但两种给药方案的病死率及临床治愈率无显著性差异[265-269]。

因此,在初始经验性抗感染治疗时选择单药治疗可减少抗菌药物使用量及医疗费用,降低药品不良反应和诱发耐药菌产生。单药治疗时可依据患者是否有混合感染或多重耐药高危因素,并应结合当地病原菌流行病学资料选择药物,并注意尽可能覆盖可能的病原菌;而联合用药的抗菌谱则更广,可覆盖更多病原菌,故对混合感染或可能为多重耐药菌感染者,可考虑联合用药。

推荐:VAP 患者初始经验性抗感染治疗常规选用适当(恰当)抗菌谱的单药抗感染治疗;若考虑病原体为多重耐药致病菌,可选择抗菌药物的联合治疗(1B)

(二)抗菌药物目标性治疗

抗菌药物的目标性治疗是在充分评估患者的临床特征并获取病原学培养及药敏结果的前提下,按照致病菌药敏结果给予相应的抗菌药物进行针对性治疗的一种策略。在 VAP 经验性抗感染治疗的基础上,一旦获得病原学证据应及时转为目标性治疗。

目前的研究资料表明,VAP 的致病菌,尤其是晚发 VAP 的致病菌多为 MDR、泛耐药(Extensively Drug-Resistant,XDR)或全耐药(Pandrug-Resistant,PDR)细菌,包括铜绿假单胞菌、鲍曼不动杆菌、MRSA 及产 ESBL 的大肠埃希菌或肺炎克雷伯菌等。本指南依据现有的国内外研究资料,结合我国流行病学特点[270-272],提出常见耐药菌的抗感染治疗策略,见表 2。

铜绿假单胞菌是目前临床最常见的 VAP 致病菌(尤其是晚发 VAP)。由铜绿假单胞菌感染所致的 VAP,在接受单药治疗时有 30% ~50% 可产生耐药菌,但亦无证据表明联合用药可减少或避免耐药菌的产生[273]。鉴于联合用药可降低不充分治疗及无效治疗的发生率,故对病情危重的 MDR 铜绿假单胞菌感染者,可参照表 4 ~2 选择抗菌药物的联合治疗。

鲍曼不动杆菌临床检出率逐年增高,尽管耐碳青霉烯类鲍曼不动杆菌的增多使得临床治疗面临越来越多的困难,但目前流行病学资料显示,鲍曼不动杆菌对碳青霉烯类、舒巴坦复合制剂、氨基糖苷类、四环素类以及多粘菌素等抗菌药物仍有较高的敏感率[274-280]。临床治疗时应尽可能根据药敏结果选用抗菌药物。而针对 MDR 鲍曼不动杆菌感染引起 VAP 的治疗,目前仅有非对照小样本临床病例观察或个案报道,尚无高质量证据,但在治疗泛耐药鲍曼不动杆菌(Extensively Drug Resistant A. baumannii,XDRAB)、全耐药鲍曼不动杆菌(Pan Drug Resistant A. baumannii,PDRAB)感染引起的 VAP 时,仍主张选择两类或三类抗菌药物进行适当的联合治疗[281]。

大肠埃希菌和肺炎克雷伯菌是最常见的产超广谱-β 内酰胺酶(Extended-spectrum Beta-lactamases,ESBL)的革兰阴性杆菌。回顾性研究分析显示,使用第三代头孢菌素类药物可增加产 ESBL 耐药菌感染的机会,故临床治疗 ESBL 耐药菌时,应避免单独使用第三代头孢菌素类药物。而第四代头孢菌素类药物的使用如头孢吡肟仍存在争议,因此对有第三代头孢菌素类药物用药史者可选用碳青霉烯类药物[282-284]。此外,β-内酰胺类/β-内酰胺酶抑制剂复方制剂为目前常用的药物。近几年肠杆菌及肺炎克雷伯杆菌对碳青霉烯类药物的耐药增加,替加环素仍有较高的敏感率,故替加环素亦可作为一种治疗选择。由于产 ESBL 肠杆菌易对氨基糖苷类及氟喹诺酮类药物产生耐药,目前尚不能确定联合用药是否能让患者获益。

MRSA 是晚发 VAP 的常见致病菌,目前临床上常用的药物有万古霉素、替考拉宁、利奈唑胺,但尚无足够证据证实哪一类药物是治疗 MRSA 引起 VAP 的最佳选择。多项 RCT 研究分别对万古霉素和利奈唑胺治疗 MRSA 所致 VAP 的临床疗效进行评估,结果显示,两者在临床治愈率、病死率及不良反应发生率均无显著差异,但利奈唑胺的微生物学总治愈率显著高于万古霉素,可能与利奈唑胺具有较强的肺组织穿透性有关[285-290]。根据近年 MRSA 的 MIC 值的变化趋势,万古霉素谷浓度达到 15 mg/L 或更高时,临床治疗可取得较好

的疗效，尽管目前缺乏有关的高质量研究，临床使用万古霉素时仍应根据患者的病理生理及药代动力学/药效学（Pharmacokinetic-pharmacodynamic，PK/PD）等计算其个体给药剂量，尽可能保证谷浓度在 15～20 mg/L。对 MRSA 与 G-菌的混合感染以及肝肾功能不全的患者，可选择替加环素进行治疗。

由于危重患者的病理生理状态与非危重者明显不同，引起 VAP 的 MDR/PDR 可选择的敏感药物甚少，其 MIC 值也较高，故在制定目标性抗菌治疗方案时，除考虑抗菌药物品种的选择外，还应尽量根据该药体内 PK/PD 特点，确定给药剂量和用药方法，以获得更好的临床疗效。PK/PD 相关因素包括：药物的作用方式（时间/浓度依赖）、药物表观分布容积与蛋白结合率；患者的病理生理状况（是否存在严重毛细血管渗漏）、血浆蛋白水平以及脏器功能（循环、肝脏、肾脏等）情况；患者接受的治疗手段［连续性肾脏替代治疗（CRRT）、人工膜氧合（ECMO）］等；再结合病原菌的 MIC 值综合制定给药方案[291]。如条件许可，治疗过程中应监测血药浓度以保证其维持在有效的治疗浓度范围内。

（三）经气管局部使用抗菌药物

对 MDR/PDR 感染（如铜绿假单胞菌或鲍曼不动杆菌）引起的 VAP，使用全身抗菌药物的治愈率不高，有研究报道治愈率甚至低于 50%[292]，其中一个重要原因在于通过静脉给药时，药物到达肺组织的浓度并不理想，而提高用药剂量又可能增加药物的毒副作用。经气管局部使用抗菌药物，可有效提高肺组织的药物浓度，同时减少全身用药的相关副作用[293-294]。有研究表明[295-296]，局部用药时气管分泌物的药物峰浓度可达到静脉用药的 200 倍，血浆谷浓度在可接受范围内，其支气管分泌物的药物谷浓度可保持在其 20 倍以上。理论上讲局部药物浓度远超过 VAP 常见病原菌的最小抑菌浓度。

除此之外，药物微粒大小、pH 值、黏稠度及雾化装置工作方式等均可影响雾化的临床疗效。其中，雾化微粒平均直径决定药物沉积部位，如直径 <1 μm 易随呼气气流被清除，>20 μm 则只沉积在鼻、咽、喉及上部气管，而在 1～5 μm 是最适宜的，可使药物沉积在细支气管及肺泡。常用的雾化装置包括超声雾化、喷雾、吸气增强型喷雾以及振荡筛喷雾，其中超声雾化的药物平均微粒直径在 3.0～3.6 μm，流速低，颗粒小，浓度高，尤其适用于插管患者[297]。

目前，最常使用的雾化抗菌药物为氨基糖苷类药物（如妥布霉素、庆大霉素、阿米卡星），也有少数研究使用头孢他啶、万古霉素、美罗培南、多粘菌素等。现有的随机对照研究显示[298-304]，与单纯静脉用药比，联合雾化吸入抗菌药物可提高 VAP 的治愈率，但并不降低病死率。然而，雾化吸入抗菌药物相关的副作用值得关注，常见的副作用包括：支气管痉挛、气道梗阻、室上性心动过速。另外有观察性的研究报道，雾化吸入抗菌药物可增加多重耐药菌发生的风险。但近年 RCT 研究结果却未证明此点[298-304]。

现有证据并不能确定雾化吸入抗菌药物在治疗 VAP 中的疗效，同时在药物种类选择、剂量、疗程等方面各项研究间有很大的差异。故雾化吸入抗菌药物不应作为 VAP 常规治疗，但对全身用药效果不佳的多重耐药非发酵菌感染者，可作为辅助治疗措施。

建议：对多重耐药的非发酵菌肺部感染，全身抗感染治疗效果不佳时，可考虑联合雾化吸入氨基糖苷类或多粘菌素类等药物治疗（2C）

（四）抗菌药物的使用疗程

1. 抗感染治疗疗程：抗感染治疗的疗程是否恰当极其重要，过短的抗感染治疗疗程可因未能清除致病菌导致治疗失败或肺炎复发。过长的疗程不仅使病原菌清除效益下降，且增加诱发耐药机会，同时也会增加脏器负担，增加医疗费用及较多的药物不良反应。Chastre 等[305]比较了 VAP 抗感染治疗 8 d 和 15 d 的疗程，结果显示，8 d 组和 15 d 组在机械通气时间、ICU 留治时间和病死率方面无差异，但在非发酵菌感染者中，8 d 组的临床肺部感染评分（Clinic PulmonaInfection Score，CPIS）高于 15 d 组。Gilles 等的研究结果亦显示[306-308]，若能对临床及微生物学进行密切监测，VAP 患者的抗感染短疗程（<10 d）较长疗程（≥10 d）更安全，病死率无显著差异，但肺炎复发率可能增加。

抗感染疗程需结合患者感染的严重程度、潜在的致病菌、临床疗效等因素做出决定。短疗程适用于初始经验性抗感染治疗恰当、单一致病菌感染、无脓肿及免疫功能正常者。而初始抗感染治疗无效、多重耐药菌感染、有复发风险高及免疫缺陷者，则不适合短疗程抗感染治疗。

推荐：VAP 抗感染疗程一般为 7～10 d，如患者临床疗效不佳、多重耐药菌感染或免疫功能缺陷则可适当延长疗程（治疗时间）（1B）

2. 抗感染治疗的降阶梯治疗：降阶梯治疗策略已成为重症感染患者抗菌药物治疗的国际共识。研究显示，降阶梯治疗同样适用于 VAP 患者，3 项观察性试验研究认为，与持续使用广谱抗菌药物治疗相比，接受降阶梯治疗虽不能缩短 ICU 留治时间，但可有效提高初始经验性治疗抗菌药物品种选择合理率及降低肺炎复发率，但不影响病死率[309-311]。提示，对 VAP 患者行抗菌药物初始经验性治疗 48～72 h 后，需及时评估患者临床情况，根据细菌学监测及药敏试验结果调整为可覆盖病原菌、窄谱、安全及经济效益比值高的药物。

推荐：VAP 患者抗感染治疗推荐降阶梯治疗策略（1C）

3. 动态监测血清降钙素原（PCT）/CPIS：血清 PCT 在严重细菌感染时水平明显升高，动态观察其变化有助于评估抗菌疗效，连续监测可指导抗菌药物使用策略。血清 PCT < 0.25 μg/L 时可不使用或停止使用抗菌药物；血清 PCT 0.25～0.5 μg/L 或与治疗前相比下降幅度≥80% 可采取降阶梯或停止使用抗菌药物；血清 PCT≥0.5 μg/L 或与治疗前相比下降幅度 <80% 可继续沿用原抗菌治疗方案；血清 PCT 水平≥0.5 μg/L 或高于治疗前水平，则应更换抗菌药物。2 项 RCT 研究表明[312-313]，根据以上原则调整抗菌药物使用方案，可显著缩短抗菌药物使用天数，减少抗菌药物暴露，且不

影响病死率及住院天数。因此,运用血清 PCT 水平变化指导 ICU 严重细菌感染(包括 VAP)的抗菌治疗策略,可减少抗菌药物暴露及选择压力,有利于确定适宜的用药疗程。

CPIS 是一项综合了临床、影像和微生物学指标,用于评估肺炎的严重程度、抗感染疗效和预后的评分系统。Singh 等[314]采用 CPIS 评分对 ICU 患者抗感染治疗效果进行研究,其方法为 CPIS >6 分者连续 10 ~ 21 d 抗感染治疗;CPIS ≤6 分者给予环丙沙星单药治疗,3 d 后再次评估仍≤6 分者则停药。该研究发现,在 CPIS 指导下进行的抗感染治疗,不仅减少抗菌药物暴露和降低治疗费用,还可显著降低抗菌药物耐药和二重感染发生,但不影响病死率。可见,CPIS 对临床医师选择抗菌药物、决定抗感染疗程同样具有指导意义。

二、应用糖皮质激素

糖皮质激素用于治疗 VAP 的研究较少,目前仅有 1 项前瞻性对照试验的研究对象涵盖 VAP 患者,该研究比较两组 ICU 肺炎患者,一组确诊后即开始甲泼尼龙治疗,另一组未使用糖皮质激素,结果发现,使用糖皮质激素组 28 d 病死率更高[315]。如果肺炎患者合并或继发感染性休克,可按照感染性休克的治疗原则加用糖皮质激素[316-318]。总之,对危重患者使用糖皮质激素治疗应谨慎,尤其在无充分证据支持时,使用糖皮质激素激素可能增加患者的死亡风险。

推荐:VAP 治疗不推荐常规应用糖皮质激素(1C)

三、应用物理治疗

胸部物理治疗是指采用物理方法可预防或减少气道内分泌物淤滞,防止发生肺部并发症,改善患者肺功能。传统的物理治疗方法包括体位引流、胸部扣拍、呼吸锻炼等。目前仅 1 项 RCT 研究[319]提示,物理治疗并不能改善 VAP 患者的临床症状和预后(如通气时间、ICU 留治时间及病死率)。然而对某些特殊人群患 VAP 时,如可耐受物理治疗,或常规治疗不能对下气道分泌物进行充分引流时,物理治疗可使其获益,但更多的证据需有进一步研究证实[320]。因此,虽无证据证明物理治疗可改善肺炎患者预后,但早期物理治疗可能有助患者的早期康复。

表 2　VAP 常见病原菌目标治疗的抗菌药物选择表

病原菌	可选择的药物
铜绿假单胞菌	• 头孢菌素类药物(如头孢哌酮、头孢他啶、头孢吡肟)或 • 碳青霉烯类(如亚胺培南、美罗培南)或 • β-内酰胺类/β-内酰胺酶抑制剂(如头孢哌酮/舒巴坦、哌拉西林/他唑巴坦) 可联合使用 • 抗假单胞菌的喹诺酮类(环丙沙星、左氧氟沙星)或 • 氨基糖苷类(如阿米卡星、庆大霉素)
• 鲍曼不动杆菌	• 含舒巴坦的 β-内酰胺类复方制剂(如头孢哌酮/舒巴坦,氨苄西林/舒巴坦)或 • 碳青霉烯类(如亚胺培南、美罗培南) 可联合使用 • 氨基糖苷类(如阿米卡星)或 • 四环素类(如米诺环素、多西环素、替加环素)或 • 喹诺酮类(如左氧氟沙星、环丙沙星)或 • 多粘菌素 E
• 产 ESBL 肠杆菌	• β-内酰胺类/β-内酰胺酶抑制剂(如哌拉西林/他唑巴坦、头孢哌酮/舒巴坦或 • 碳青霉烯类 (如美罗培南、亚胺培南) • 四环素类(如替加环素)
• 甲氧西林耐药的金黄色葡萄球菌	• 利奈唑胺或 • 糖肽类(如万古霉素,替考拉宁) • 四环素类(如替加环素)

注:VAP:呼吸机相关性肺炎

附录 1:呼吸机相关性事件(Ventilator-Associated Events, VAE)的新监控方法

VAP 一直作为医疗保健相关性感染事件中装置(?)相

表 1　VAP 常见可能致病菌与初始经验性治疗抗菌药物选择建议表

	可能的病原菌	可选择药物
早发 VAP(≤4 d)、不存在或低多重耐药菌感染高危因素	• 肺炎链球菌 • 流感嗜血杆菌 • 抗菌药物敏感的 G-肠杆菌 大肠埃希菌 肺炎克雷伯菌 变形杆菌 沙雷菌 • 甲氧西林敏感的金黄色葡萄球菌	• 广谱青霉素/β-内酰胺酶抑制剂(如阿莫西林/克拉维酸钾、氨苄西林/舒巴坦)或 • 第二代/第三代头孢菌素类药物(如头孢呋辛、头孢噻肟)或 • 喹诺酮类(如左氧氟沙星、莫西沙星、环丙沙星)或 • 窄谱碳青霉烯类(如厄他培南)
晚发 VAP(≥5 d)、存在高多重耐药菌感染高危因素:(1)90 d 内曾使用抗菌药物;(2)入院超过 5 d;(3)居住在耐药菌高发的社区或特殊医疗机构;(4)正在接受免疫抑制治疗或存在免疫功能障碍	• 上述病原菌 • 铜绿假单胞菌 • 肠杆菌科菌(产 ESBL)如肺炎克雷伯菌 • 不动杆菌属 • 甲氧西林耐药的金黄色葡萄球菌	• 头孢菌素类药物(如头孢哌酮、头孢他啶、头孢吡肟)或 • 碳青霉烯类(如亚胺培南、美罗培南)或 • β-内酰胺类/ • β-内酰胺酶抑制剂(如头孢哌酮-舒巴坦、哌拉西林-他唑巴坦) 考虑 G^- 耐药菌感染可联用:(1)喹诺酮类(如环丙沙星、左氧氟沙星);(2)氨基糖苷类(如阿米卡星、庆大霉素) 考虑 G^+ 耐药菌感染可联用:(1)利奈唑胺;(2)糖肽类(如万古霉素、替考拉宁)

注:VAP:呼吸机相关性肺炎

关性感染的一个重要监控指标，但 VAP 诊断标准主观性大，诊断方法特异性低，临床诊断困难，不利于 VAE 的监控。为此，近年来，CDC（中文）（Centers for Disease Control and Prevention）提出了一个新的 VAE 监测方法，可监控更大范围的呼吸机相关人群或并发症。凡年龄≥18 岁，急症、需长期重症监护或行康复治疗的机械通气超过 3 d 的住院患者（常规机械通气效果欠佳的危重患者除外）均应纳入监控范围。纳入后，根据患者临床症状及实验室数据，按步骤逐步判断或根据病情发展持续跟踪。

VAE 监控流程：机械通气时间≥3 d→病情稳定或治疗有效，但随后出现氧合功能持续恶化→呼吸机相关性条件（VAC）感染或炎症的一般证据→感染性呼吸机相关性并发症（IVAC）→微生物学检查阳性→可能或很可能为呼吸机相关性肺炎（VAP）。患者机械通气时间≥3 d，而同时在病情稳定或治疗有效后，出现氧合功能（?）持续恶化，认为其处于呼吸机相关性条件（Ventilator-Associated Condition，VAC）状态；如患者进一步出现体温 > 38℃ 或 < 36℃，外周血（?）白细胞计数≥12 000 细胞/mm^3（?）或≥4000 细胞/mm^3（?）等感染一般证据，则提示患者已为（出现？并发?）感染性呼吸机相关性并发症（Infection-Related Ventilator-Associated Complication，IVAC）；在此状态下，如气管抽吸物、支气管肺泡灌洗液等微生物学检查阳性，则可能或很可能已发展为 VAP。

依据以上流程逐步判断有助于医护人员清晰、准确地完成 VAE 各项监测指标，包括 VAC、IVAC 及以往诊断困难的 VAP。而对病情不断发展的患者持续追踪可对该类 VAP 高发人群重点监控，采用各项措施防止其最终发展为 VAP。

附录 2

1. 指南制定流程：在全面检索文献的基础上，采用严谨的文献评价体系（GRADE，Grades of Recommendations Assessment，Development and Evaluation）制定循证指南的策略。本指南依据 GRADE 制作流程，分 6 个阶段：（1）确定指南撰写的内容分为诊断、预防和治疗三大专题板块，证据质量评估的方法采用 GRADE 方法，指定每个专题的负责人和成员，成立相应的工作小组。（2）循证医学小组对所有的工作小组成员进行循证指南制定策略培训、文献检索培训、和文献证据质量评估方法（GRADE 方法）培训，并参与整个指南制定过程和解答相关问题。（3）各个专题工作小组再分成两组人员，各自独立检索文献、对文献进行筛选、对证据质量进行初步评估，并拟定初定的推荐级别。（4）工作小组的两组人员针对每个具体问题和干预措施，就纳入的文献、证据质量分级和推荐分级等方面通过邮件和开会等形式进行研究讨论，讨论后确定指南草稿。（5）每个专题板块的负责人再把指南草稿以邮件的形式发给指南工作组各位专家，对文献质量和推荐级别进行审查。⑥指南工作组召集指南专家研讨会，进行讨论、表决和修改，最后制定指南修订稿。

2. 文献筛选和收集：选用的数据库：（1）英文：pubmed/medline，Embase 和 The Cochrane Central Register of Controllled Trials（CENTRAL）；（2）中文：万方数据库和中国知网。时间：1990 年 1 月—2012 年 12 月。工作小组针对每个具体临床问题制定不同的检索词，检索词至少要包括：英文：ventilator associated pneumonia，hospital acquired infection，mechanical ventilation/artificial airway；中文：呼吸机相关性肺炎，院内感染，机械通气/人工气道。

3. GRADE 方法：本指南采用 GRADE 方法，对证据质量和推荐强度进行分级。GRADE 方法为卫生保健领域的系统评价和指南总结证据提供了一种透明的结构化方法[321-341]。与其他分级系统相比具有如下优势[322]：（1）由一个具有广泛代表性的国际指南制定小组制定；（2）明确界定了证据质量和推荐强度；（3）清楚评价了不同治疗方案的重要结局；（4）对不同级别证据的升级与降级有明确、综合的标准；（5）从证据到推荐全过程透明；（6）明确承认价值观和意愿；（7）就推荐意见的强弱，分别从临床医生、患者、政策制定者角度做了明确实用的诠释；（8）适用于制作系统评价、卫生技术评估及指南。

GREDE 方法把证据质量分为“高、中、低和极低”四个等级，分别用 A、B、C 和 D 表示[322]（表 1）；将推荐意见分为“强推荐和弱推荐”两个级别，分别用 1 和 2 表示[323]（表 2）。在实际操作过程中，还有一种情况是“无明确推荐意见”[326]。

表 1　证据质量及其定义

证据质量	代表符号	定义
高	A	进一步研究也不可能改变该疗效评估结果的可信度
中	B	进一步研究很可能影响该疗效评估结果的可信度，且可能改变该评估结果
低	C	进一步研究极有可能影响该疗效评估结果的可信度，且该评估结果很可能改变
极低	D	任何疗效评估结果都很不确定

表 2　推荐强度和含义

推荐强度	代表符号	含义
强推荐	1	（1）对患者——在这种情况下，多数患者会采纳推荐方案，只有少数不会；此时若未予推荐，则应说明。 （2）对临床医生——多数患者应该接受该推荐方案。 （3）对政策制定者——该推荐方案在大多数情况下会被采纳作为政策。
弱推荐	2	（1）对患者——在这种情况下，大多数患者会采纳推荐方案，但仍有不少患者不采用。 （2）对临床医生——你应该认识到不同患者有各自适合的方案，你得帮助每个患者做出体现他（她）价值观和意愿的决定。 （3）对政策制定者——制定政策需要实质性讨论，并需要众多利益相关者参与。
无明确推荐意见		利弊相当。 未确定目标人群。 制定推荐意见的证据不足。

制定推荐意见的 GRADE 方法分 3 个步骤[328]，参见文献[323-326,328-336,338]。决定推荐强度有四个关键因素[323,325]（表 3）。

意见不一致时，采用下述投票程序[326]：（1）对持续存在分歧的部分，推荐或反对某一干预措施（和特定的替代措施相比较）至少需要 50% 的参与者认可，少于 20% 选择替代措施（选择认为是平等的）。未满足此项标准将不产生推荐意见。（2）一个推荐意见被列为强推荐而非弱推荐，则需要得到至少 70% 的参与者认可。

表 3　推荐强度的决定因素

因素	说明
利弊平衡	利弊间的差别越大,越适合作出强推荐;差别越小,越适合作出弱推荐。
证据质量	证据质量越高,越适合作出强推荐。
价值观和意愿	价值观和意愿差异越大,或不确定性越大,越适合作出弱推荐。
成本(资源配置)	干预措施的成本越高(即消耗的资源越多),越不适合作出强推荐。

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