Bojan Jovanović[1], Adi Hadžibegović[1], Jovana Avramović[1],
Milan Savić[2], Ivan Rović[1], Đuro Šijan[1], Nebojša Brezić[1],
Jovana Antonijević[1], Sofija Mirosavljević[1]

BOLNIČKE PNEUMONIJE

Sažetak: Nozokomnijalne (bolničke) pneumonije se definišu kao pneumonije kod pacijenata koji su hospitalizovani i koje se javljaju unutar 48h nakon prijema u bolnicu ili kasnije. Ova vrsta infekcije plućnog parenhima izazvana je patogenima koji su prisutni u bolničkoj sredini. Inkubacioni period nije duži od dva dana. Nozokomnijalne pneumonije se po učestalosti nalaze na drugom mestu u odnosu na sve bolničke infekcije i najviša prevalencija se beleži u jedinicama intenzivnog lečenja (JIL) (internističkim i hirurškim). One predstavljaju veliko opterećenje za zdravstveni sistem svuda u svetu jer je procenjeno da čak 25% infekcija u JIL su bolničke, a da se 50% svih antibiotika primenjuje upravo za njihov tretman.

Prepoznavanje uzročnika može biti izazovno, pre svega zbog težine adekvatnog uzorkovanja sputuma, ali i nerazumevanja epidemiološke situacije u određenoj zdravstvenoj ustanovi.

Ključne reči: pneumonije, infekcija, rezistencija

Uvod

Definicija nozokomnijalne pneumonije se menjala poslednjih nekoliko decenija. Američko udruženje torakalnih hirurga (The American Thoracic society - ATS) je prvi put 1996. godine objavilo preporuke za dijagnostiku i tretman bolničkih pneumonija.[1] Već 1998. godine Trouillet-e i saradnici su preporučili klasifikaciju pacijenata sa VAP-om na osnovu faktora rizika sa ciljem za racionalnu primenu inicijalne antibiotske terapije.

[1] Bojan Jovanović, Urgentni centar, Univerzitetski klinički centar Srbije, Služba anesteziologije i intenzivne medicine, bjovanovic@outlook.com

[2] Klinika za grudnu hirurgiju, Univerzitetski klinički centar Srbije

Epidemiologija

U značajnoj internacionalnoj studiji (EPIC II) dokazano je da čak 51% pacijenata u jedinicama intenzivnog lečenja ima infekciju.[2] Kao i za sve bolničke infekcije, incidencija i prevalencija se razlikuju između centara, pa čak i između jedinica intenzivnog lečenja u istoj ustanovi. U proseku, incidencija iznosi 9–27%, što je 1.2 do 8.5 slučajeva na 1000 dana mehaničke ventilacije (29, 30, 2). Na incidenciju primarno utiče starosna dob bolesnika. Kod mlađih od 35 godina incidencija je 5 na 1000 slučajeva hospitalizacije, dok je kod populacije starijih od 65 godina ta incidencija čak 15 na 1000 slučajeva.[3-5]

Procenjeno je da se rizik za nastanak VAP-a povećava za 1% po danu mehaničke ventilacije u proseku, ali je najveći u prvih 5 dana (oko 3%) i smanjuje se na 2% po danu od 5. do 10. dana mehaničke ventilacije i 1% nakon desetog dana.

Podela

Pneumonije mogu biti primarno endogene (patogen je izolovan na prijemu), sekundarno endogene (kolonizacija patogena orofarinksa i gastrointestinalnog trakta tokom hospitalizacije, koja kasnije dovodi do translokacije u donje partije disajnog puta) i egzogene (kolonizacija nastaje usled mehaničke ventilacijem, npr. tubusi, ovlaživači, bronhoskop i patogen nije primarno izolovan na pacijentu na prijemu).[6]

Pneumonija povezana sa mehaničkom ventilacijom (ventilator-associated pneumonia – VAP) je vrsta bolničke pneumonije koja se može javiti 48 sati nakon intubacije pacijenta. Nastaju u jedinicama intenzivnog lečenja i karakteriše se prisustvom novog ili progresivnog infiltrata na Rtg snimku pluća, znacima sistemske infekcije (povišena telesna temperatura, leukocitoza ili leukopenija), promenom u karakteristikama sputuma i detekcijom uzročnika (patogena). VAP su najčešće bolničke infekcije u JIL.[7]

VAP se deli na rani i kasni u zavisnosti od vremenskog perioda od započinjanja mehaničke ventilacije. Podela je od značaja jer su u mnogim studijama prouzrokovači bili različiti, te se i inicijalni empirijski tretman razlikuje, a utiče i na ishod. Rani VAP nastaje tokom prva 4 dana, a kasni nakon tog perioda. Međutim, mnoge studije su poredile različite vremenske periode (pragove) za rani i kasni VAP. Poredeći četvrti, peti i sedmi dan kao prag za razlikovanje ranog i kasnog VAP-a Gastmeier i saradnici su još 2009. godine došli do zaključka da ne postoji značajna razlika u izolovanim patogenima u sve tri grupe, da pojava multirezistentnih bakterija ne zavisi od ove podele već od ukupnog broja dana na mehaničkoj ventilaciji, i da ta podela nema klinički značaj.[8-10]

Pneumonija povezana sa medicinskim osobljem (Healthcare-associated pneumonia – HCAP) se definiše kao pneumonija kod osobe koja je u prethodnih 90 dana bila hospitalizovana najmanje dva dana, boravi u ustanovama za negu (u staračkom

domu), ili je bila u ustanovama za kratkotrajne intervencije, zatim kod osoba kod kojih se primenjuje terapija u kućnim uslovima (vrši je terenska služba, npr. kućna obrada rane, primena antibiotika), kod kojih je vršena hronična dijaliza (na programu hr. dijalize) u prethodnih 30 dana, kao i ako osoba živi u domaćinstvu u kome je neki član inficiran i/ili kolonizovan multirezistentnom bakterijom. Pored navedenog, ova pneumonija se odnosi i na pneumonije koje se javljaju nakon tri dana od primene određenog antibiotika u određenoj zdravstvenoj ustanovi, primene hemioterapije ili bilo koje vrste obrade rane.[11]

Poslednjih nekoliko godina promene u zdravstvenom sistemu dovele su do toga da mnogi pacijenti, naročito hronični bolesnici, budu zbrinuti van ustanova (npr u kućnim uslovima). Time je razlika između vanbolničkih infekcija (community infections) i bolničkih infekcija postala manje jasna. Pacijenti su i van bolnica u kontaktu sa zdravstvenim osobljem. Rezultat toga je veći mortalitet kod HCAP zbog neadekvatne inicijalne antibiotske terapije usled prisustva multirezistentnih sojeva.

Dijagnoza

Još uvek ne postoji univerzalno prihvaćen, zlatni standard za postavljanje dijagnoze VAP-a jer nijedna klinička metoda nije pokazala značajnu senzitivnost i specifičnost.[12] Jedini pouzdan metod za rano dijagnostikovanje je svakodnevna klinička procena uz radiografsko praćenje.

Ona podrazumeva novi, perzistentni infiltrat na Rtg snimku pluća nakon 48 sati od prijema koji ne može drugačije da se objasni, praćen sa jednim sistemskim i dva plućna (respiratorna) kriterijuma. Sistemski kriterijumi su: telesna temperatura > 38°C, leukocitoza (broj leukocita > 12.000/mm^3) ili leukopenija (broj leukocita < 4.000 mm^3) i izmenjen mentalni status kod starijih od 70 godina bez drugog očiglednog uzroka. Plućni kriterijumi uključuju: 1. pojavu purulentnog sputuma (ili promenu u kvalitetu sputuma, povećanu sekreciju ili povećanu potrebu za aspiracijom), 2. pogoršanje gasnih analiza (pad saturacije, povećanje inspiratorne frakcije kiseonika – FiO2, povećana potpora mehaničke ventilacije), 3. kašalj ili pogoršanje kašlja, dispnea ili tahipnea, 4. auskultatorni nalaz na plućima (rales or bronchial breath sounds).[13-16]

Međutim, kliničkom procenom se ne dijagnostikuje čak trećina slučajeva VAP-a, što je dokazano na obdukcijama, a u više od 50% slučajeva može biti netačna. Dakle, klinički kriterijumi imaju samo 69% senzitivnost i 75% specifičnosti. CDC definicija VAP-a je podložna varijabilnosti među lekarima koji ih tumače i subjektivnosti. Zbog toga je pokušana primena pojednostavljene verzije nadzora pacijenata za nastanak pneumonije, koja se odnosila prvenstveno na parametre oksigenacije.[17,18] Pogoršanje parametara oksigenacije definisali su na sledeći način: nakon dva dana stabilnog perioda vrednosti PEEP-a (ili smanjenja PEEP-a svakog dana) sledio je period povećanja PEEP-a za 2.5 cmH2O za više od dva dana, ili nakon perioda normalnih vrednosti

FiO2 sledio je period povećanja FiO2 za najmanje 0.15 bar dva dana. VAP je bio dijagnostikovan značajno brže (3.5 vs. 39 minuta za dijagnostikovanje po pacijentu), iako nije bilo razlike u mortalitetu, boravku u ICU i na mehaničkoj ventilaciji.[19]

Validnost kliničke procene za dijagnostikovanje i dužinu primene antibiotske terapije je nedavno proverena u studiji Kalanuria i sar. u neurohirurškim jedinicama intenzivnog lečenja, gde je primećena varijabilnost u dužini terapije VAP-a i prekomernoj upotrebi antibiotika među kliničarima. Jedna grupa pacijenata je dijagnostikovana i primala terapiju na osnovu kliničke procene, a kod druge grupe su primenjeni kriterijumi od strane CDC po protokolu. Samo 31,3% lečenih pacijenata je imalo ispunjene kriterijume CDC. Primećena je, takođe, značajna duža primena antibiotika samo na osnovu kliničke procene, iako nije bilo razlike u mortalitetu između navedenih grupa.[20-25]

Radiološka dijagnostika

RTG snimak pluća nije uvek pouzdan, jer postoje mnoga druga stanja koja mogu da daju sličan nalaz: pneumonitis, kongestivne promene, atelektaza, efuzija, hemoragija, kontuzija, pa čak i akutni respiratorni distres sindrom. Dokazana je loša (slaba) korelacija radioloških nalaza i histopatološke dijagnoze pneumonija. Takođe, interpretacija radiološkog nalaza je nekada otežana kod intubiranih, kritično obolelih pacijenata. Tipičan primer su studije koje su dokazale da snimak pluća može biti normalan, ali se tek na CT nalazu vide infiltrati, što se može desiti kod pacijenata sa HOBP. Nijedan radiološki znak za pneumoniju kod intubiranih pacijenata nema dijagnostičku preciznost veću od 68%. Međutim, u metaanalizi Kolmpas i sar. pokazano je da odsustvo kliničkih parametara, kao što su povišena temperatura, leukocitoza i purulentna sekrecija, ne isključuju dijagnozu VAP-a, dok odsustvo pozitivnog radiološkog znaka značajno smanjuje verovatnoću postojanja pneumonije. Takođe, VAP treba razlikovati od traheobronhitisa, a jedino prisustvo hipoksije i/ili infiltrata (konsolidacije) na Rtg snimku pluća mogu da budu od značaja za to.[26]

Uzorkovanje sputuma i analiza

Uzorkovanje se vrši na nekoliko načina, bronhoskopskom ili nebronhoskopskom metodom (manje invazivnom). U invazivne metode spadaju bronhoalveolarna lavaža (BAL) i protected specimen brush (PSB), dok su endotrahealna aspiracija i mini-BAL nebronhoskopske metode.

Bronhoalveolarna lavaža se izvodi plasiranjem bronhoskopa do nivoa subsegmentnog bronha (3. i 4. generacija bronha), dok se ne okludira lumen. Zatim

se ubrizga 20–50 ml sterilnog fiziološkog rastvora (mada neki autori koriste i veću količinu, 100–240 ml) i ponovo aspirira sadržaj iz distalnih partija respiratornog trakta. Oko 5 ml dobijenog uzorka je dovoljno za mikrobiološku analizu. Mini-BAL predstavlja metodu kojom se aspiracionim kateterom plasira kroz endotrahealni tubus dok se ne naiđe na otpor i zatim se ubrizga fiziološki rastvor, koji se zatim aspirira i taj se sadržaj pošalje na analizu.[27]

Mini-BAL tehnikom se rutinski uzimaju uzorci i upotrebom automatozovane mikroskopije sa 100% senzitivnosti postavlja dijagnoza VAP-a kod pacijenata sa visokim rizikom.

PSB je tehnika kojom se specijalnom četkicom dopire najdistalnije moguće, i uzorkovanje je preciznije. Uzorak četkicom je do 0.01 ml i zato se razblažuje sa 1 ml Ringerovim rastvorom. Prag za kvantitativnu dijagnozu je u ovom slučaju 10^3 cfu/ml.[28]

Endotrahealna aspiracija je bez sumnje najbrža, najlakša i najjeftinija metoda uzorkovanja. Iako rezultat uzorkovanjem ima visoku senzitivnost, specifičnost je izuzetno niska (14–47%) i zato se takav uzorak kvantitativno analizira. Tokom endotrahealne aspiracije aspiracioni kateter se plasira preko endotrahealnog tubusa dok se ne naiđe na otpor, i zatim se aspirira sadržaj koji se šalje na mikrobiološku analizu.[29-35]

Dakle, analiza uzorka može biti kvantitativna ili kvalitativna. Iako kvantitativna analiza ima veću specifičnost u postavljanju dijagnoze VAP-a, mogu se dobiti ili lažno negativni rezultati kod pacijenata sa ranim VAP-om sa neadekvatnom antibiotskom terapijom ili lažno pozitivni, pri kolonizaciji tokom mehaničke ventilacije. Bronhoskopskim metodama prag za postavljanje dijagnoze VAP-a je niži (kod BAL 10^4 cfu (kolonija)/ml i PSB 10^3 cfu/ml), dok je taj prag za uzorak dobijen endotrahealnom aspiracijom 10^6 cfu/ml.

Terapija

Terapija bolničkih pneumonija se bazira na poznavanju epidemiološke situacije u određenoj bolnici ili jedinici intenzivnog lečenja. Osnova uspešnog tretmana je uvek multidisciplinarni pristup koji podrazumeva učešće infektologa, epidemiologa, mikrobiologa, kao i anesteziologa ili intenziviste.[36]

Zaključak

Bolničke pneumonije su izazov, kako za dijagnostikovanje tako i za tretman, uzimajući u obzir sve veću rezistenciju uzročnika na antibiotike, ali i nove forme adaptacije kojima se postiže veća otpornost. Poznavanje farmakodinamike i farmakokinetike antibiotika je od ključnog značaja, naročito u empirijskom tretmanu. Za

sada je još uvek od velikog značaja uključenost više lekara različitih specijalnosti u donošenju odluke koje antibiotike uključivati kao mera prevencije neadekvatnog tretmana i povećanja rezistencije.

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Bojan Jovanović[1], Adi Hadžibegović[1], Jovana Avramović[1],
Milan Savić[2], Ivan Rović[1], Đuro Šijan[1], Nebojša Brezić[1],
Jovana Antonijević[1], Sofija Mirosavljević[1]

NOSOCOMNIAL PNEUMONIA

Summary: Nosocomnial (hospital) pneumonias (hospital-acquired pneumonia - HAP) are defined as pneumonias in hospitalized patients that occur within 48 hours after admission to the hospital or later. These types of lung parenchymal infections are caused by pathogens that are present in the hospital environment. The incubation period is no longer than two days. Nosocomial pneumonias are the second most common of all hospital infections and the highest prevalence is recorded in intensive care units (ICU) (internal medicine and surgery). They represent a great burden on the health system everywhere in the world, because it is estimated that as many as 25% of infections in the ICU are hospital-acquired, and that 50% of all antibiotics are used precisely for their treatment.

Recognizing the causative agent can be challenging, primarily due to the difficulty of adequate sputum sampling, but also due to the lack of understanding of the epidemiological situation in a particular health facility.

Introduction

The definition of nosocomial pneumonia has changed in the last few decades. The American Thoracic Society (ATS) first published recommendations for the diagnosis and treatment of hospital-acquired pneumonia in 1996[1]. By 1998, Trouillet and colleagues recommended classifying patients with VAP (ventilator-associated pneumonia) based on risk factors to optimize initial antibiotic therapy.

[1] Bojan Jovanović, Urgentni centar, Univerzitetski klinički centar Srbije, Služba anesteziologije i intenzivne medicine, bjovanovic@outlook.com

[2] Klinika za grudnu hirurgiju, Univerzitetski klinički centar Srbije

Epidemiology

In a significant international study (EPIC II), it was proven that 51% of patients in intensive care units have an infection[2]. The incidence and prevalence of hospital infections vary between centers and even within intensive care units in the same institution. On average, the incidence is 9-27%, equivalent to 1.2 to 8.5 cases per 1000 days of mechanical ventilation. Patient age significantly influences the incidence, with younger than 35 years at 5 per 1000 hospitalizations and those over 65 years at 15 per 1000 hospitalizations[3-5].

The risk of VAP occurrence increases by 1% per day on average during mechanical ventilation, peaking at around 3% in the first 5 days. It then decreases to 2% per day from days 5-10 and 1% after the tenth day.

Classification

Pneumonias can be primarily endogenous (pathogen isolated on admission), secondarily endogenous (colonization of oropharyngeal and gastrointestinal pathogens during hospitalization leading to translocation to lower respiratory tract), and exogenous (colonization due to mechanical ventilation, e.g., tubes, humidifiers, bronchoscopy, and the pathogen is not primarily isolated on patient admission)[6].

Ventilator-associated pneumonia (VAP) is a type of hospital pneumonia that can occur 48 hours after intubating a patient. They occur in intensive care units and are characterized by the presence of new or progressive infiltrates on chest X-ray, signs of systemic infection, changes in sputum characteristics, and the detection of pathogens. VAP is the most common hospital infection in the ICU[7].

VAP is divided into early and late depending on the time from the start of mechanical ventilation. This division is significant because causative agents and initial empirical treatment vary, affecting outcomes. Early VAP occurs within the first 4 days, while late VAP occurs after that period. However, studies comparing different time periods for early and late VAP found no significant differences in isolated pathogens, the occurrence of multidrug-resistant bacteria, or clinical significance[8-10].

Healthcare-associated pneumonia (HCAP) is defined as pneumonia in a person who has been hospitalized for at least two days in the past 90 days, resides in nursing facilities, or has received home-based therapy. It also includes those undergoing chronic dialysis in the last 30 days or living in households where a member is infected and/or colonized by multidrug-resistant bacteria. HCAP encompasses pneumonia occurring three days after using a specific antibiotic in a healthcare facility, chemotherapy, or any wound care[11].

In recent years, changes in the healthcare system have led to a significant number of patients, especially chronic patients, being cared for outside institutions (e.g., at

home). This blurs the distinction between community and hospital infections, leading to higher mortality in HCAP due to inadequate initial antibiotic therapy in the presence of multidrug-resistant strains.

Diagnosis

There is no universally accepted gold standard for diagnosing VAP as no clinical method has shown significant sensitivity and specificity[12]. The only reliable method for early diagnosis is daily clinical assessment with radiographic monitoring. This involves a new, persistent infiltrate on a chest X-ray 48 hours after admission, accompanied by one systemic and two pulmonary (respiratory) criteria. Systemic criteria include a temperature >38°C, leukocytosis (>12,000/mm³) or leukopenia (<4,000 mm³), and altered mental status in those over 70 years without another apparent cause. Pulmonary criteria include the appearance of purulent sputum, worsening gas analysis, cough, dyspnea, or tachypnea, and abnormal lung auscultation[13-16].

However, clinical assessment alone does not diagnose a third of VAP cases, as shown in autopsies, and can be incorrect in over 50% of cases. Clinical criteria have only 69% sensitivity and 75% specificity. The CDC definition of VAP is subject to variability among interpreting physicians and subjectivity. Therefore, a simplified version of patient surveillance for pneumonia has been attempted, primarily focusing on oxygenation parameters[17,18]. Deterioration in oxygenation parameters was defined as a period of increased PEEP for more than two days after two days of stable values or an increase in FiO2 for at least 0.15 bar for two days after a period of normal FiO2 values. VAP was diagnosed significantly faster (3.5 vs. 39 minutes per patient), although there was no difference in mortality, ICU stay, and mechanical ventilation[19].

The validity of clinical assessment for diagnosis and the duration of antibiotic therapy was recently examined in a study by Kalanuria et al. in neurosurgical intensive care units. They found significant variation in VAP therapy duration and excessive antibiotic use among clinicians. Only 31.3% of treated patients met CDC criteria. There was also a significantly longer antibiotic treatment duration based solely on clinical assessment, although there was no difference in mortality between the groups[20-25].

Radiological Diagnosis

Chest X-rays are not always reliable, as many other conditions can produce similar findings: pneumonitis, congestive changes, atelectasis, effusion, hemorrhage, contusion, and even acute respiratory distress syndrome. There is a poor correlation between radiological findings and histopathological diagnosis of pneumonia. Interpretation of radiological findings is sometimes challenging in intubated, critically ill

patients. Studies have demonstrated that a chest X-ray may be normal, while infiltrates are visible on a CT scan, especially in patients with COPD. No radiological sign for pneumonia in intubated patients has a diagnostic accuracy greater than 68%. However, a meta-analysis by Kolmpas et al. showed that the absence of clinical parameters such as fever, leukocytosis, and purulent secretion does not exclude the diagnosis of VAP, while the absence of a positive radiological sign significantly reduces the likelihood of pneumonia[26].

Sputum Sampling and Analysis

Sampling can be done invasively or non-invasively, with bronchoscopic or non-bronchoscopic methods. Invasive methods include bronchoalveolar lavage (BAL) and protected specimen brush (PSB), while endotracheal aspiration and mini-BAL are non-bronchoscopic methods.

Bronchoalveolar lavage involves placing a bronchoscope to the level of subsegmental bronchi and injecting 20-50 ml of sterile saline. About 5 ml of the obtained sample is sufficient for microbiological analysis[27]. Mini-BAL involves passing an aspiration catheter through the endotracheal tube until resistance is encountered, injecting saline, aspirating the content, and sending it for analysis.

PSB is a technique that reaches the most distal point with a special brush, providing more precise sampling. The sample is diluted with 1 ml of Ringer's solution. The threshold for quantitative diagnosis in this case is 10^3 cfu/ml[28].

Endotracheal aspiration is undoubtedly the fastest, easiest, and cheapest sampling method. Although the result has high sensitivity, specificity is extremely low (14-47%), so such a sample is quantitatively analyzed. Endotracheal aspiration involves passing the aspiration catheter through the endotracheal tube until resistance is encountered, then aspirating the content sent for microbiological analysis[29-35].

Therefore, sample analysis can be quantitative or qualitative. Although quantitative analysis has higher specificity in diagnosing VAP, false-negative results can be obtained in patients with early VAP with inadequate antibiotic therapy or false positives in colonization during mechanical ventilation. Bronchoscopic methods have a lower threshold for diagnosing VAP (10^4 cfu/ml for BAL and 10^3 cfu/ml for PSB), while the threshold for samples obtained by endotracheal aspiration is 10^6 cfu/ml.

Therapy

The therapy for hospital pneumonias is based on understanding the epidemiological situation in a particular hospital or intensive care unit. A successful treatment approach always involves a multidisciplinary approach, with the participation of

infectious disease specialists, epidemiologists, microbiologists, as well as anesthesiologists or intensivists[36].

Conclusion

Hospital pneumonias pose challenges both in terms of diagnosis and treatment, considering the increasing resistance of pathogens to antibiotics and the emergence of new forms of adaptation leading to greater resistance. Understanding the pharmacodynamics and pharmacokinetics of antibiotics is crucial, especially in empirical treatment. Currently, the involvement of multiple physicians from different specialties remains crucial in deciding which antibiotics to include as a measure to prevent inadequate treatment and increased resistance.

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