Chapter 11: Pneumococcal Disease

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I. Disease Description

Streptococcus pneumoniae (pneumococcus) is a gram-positive bacteria bacterium with more than 90 known serotypes. Pneumococcus is spread by airborne droplets and is a leading cause of serious illness, including bacteremia, meningitis, and pneumonia among children and adults worldwide.[1, 2] Although all serotypes may cause serious disease, a relatively limited number of serotypes cause the majority of invasive pneumococcal disease (IPD).

The Centers for Disease Control and Prevention's (CDC) Active Bacterial Core Surveillance (ABCs) has tracked IPD in selected regions of the United States since 1994. ABCs data indicate that individuals aged <2 years and ≥65 years have the highest rates of invasive disease (Table 1).[2, 3] Approximately 10% of all patients with invasive pneumococcal disease die of their illness, but case-fatality rates are higher for the elderly and patients with certain underlying illnesses.[3, 4]

Each year in the United States, pneumococcal disease accounts for a substantial number of cases of invasive and non-invasive disease including meningitis, bacteremia, pneumonia, and acute otitis media (AOM).[3–8] A recent analysis estimated that pneumococcal disease was responsible for 4 million illness episodes, 445,000 hospitalizations and 22,000 deaths annually.[9] Pneumococcal disease is preceded by asymptomatic colonization of the nasopharynx which tends to be especially common in children.[10] Acute otitis media (AOM) is the most common clinical manifestation of pneumococcal infection among children and the most common outpatient diagnosis resulting in antibiotic prescriptions in that group.[11]

Table 1: Incidence of pneumococcal infections in the United States

Type of bacterial infection	# cases / year
Meningitis*	2,000
Bloodstream infection†	8,000
Pneumonia (hospitalized)§	106,000–175,000
Acute otitis media in children <5 yrs¶	3,100,000

* S. pneumoniae *isolated from cerebrospinal fluid or clinical diagnosis of meningitis with pneumococcus isolated from another sterile site*[2]

† *Bacteremia without focus*[2]

§ *Estimates before introduction of pneumococcal conjugate vaccine for children in 2000.*[12]

¶ *The number of doctor visits per year for acute otitis media in children younger than 5 years is estimated to be 14,106,159.*[8] *Approximately 30% of these visits probably represent otitis media with effusion and do not require antibiotics.*[9] *Recent data from etiologic studies of otitis media in two different areas of the United States suggest that approximately 31% of acute otitis media episodes are caused by* S. pneumoniae.[10, 11] *[14.1 million x 70% x 31% = 3.1 million]*

II. Background

Pneumococcal vaccines

Two different types of pneumococcal vaccines, polysaccharide and conjugate vaccines, are employed in the prevention of pneumococcal disease. Polysaccharide vaccines contain capsular pneumococcal polysaccharide antigens, while conjugate vaccines contain an immunogenic nonpneumococcal protein conjugated to individual pneumococcal polysaccharides.

A pneumococcal polysaccharide vaccine (PPV) targeting 23 of the most common serotypes of *S. pneumoniae* has been available since 1983. The Advisory Committee on Immunization Practices (ACIP) recommends that it be administered to persons ≥2 years of age who have any of several underlying medical conditions and to all persons >65 years of age.[5, 12]

In February 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was licensed by the Food and Drug Administration (FDA) for use among infants and young children. In pre-licensure randomized trials, PCV7 was demonstrated to be safe and highly efficacious

against invasive pneumococcal disease (IPD), moderately efficacious against pneumonia, and somewhat effective in reducing otitis media episodes and related office visits.[13–15] On the basis of the results of these clinical trials, in 2000, ACIP recommended routine use of PCV7 for all children aged 2–23 months and for children aged 24–59 months who are at increased risk for pneumococcal disease (e.g., children with anatomic or functional asplenia, sickle cell disease (SCD), HIV infection or other immunocompromising condition, or chronic illness including chronic heart or lung disease, cerebrospinal fluid leaks, and diabetes mellitus).[11] In 2007, the ACIP revised its recommendation for routine use to include all children aged 2–59 months.[16]

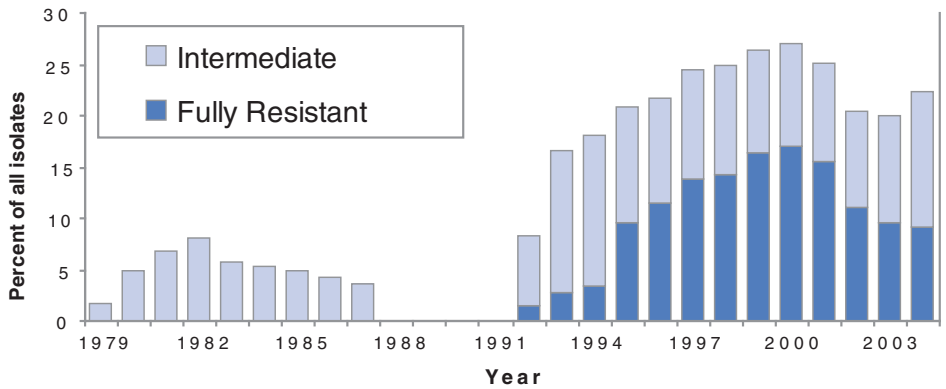
In February, 2010, a new 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the FDA and has now replaced PCV7.[17] PCV13 is formulated and manufactured using the same processes as PCV7 and was licensed by FDA on the basis of studies demonstrating safety and ability comparable to that of PCV7 to elicit antibodies protective against IPD. PCV13 is made by the same manufacturer as PCV7 and contains the seven serotypes included in PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F) as well as six additional serotypes (1, 3, 5, 6A, 7F and 19A). PCV13 is approved for prevention of IPD among infants and young children caused by the 13 serotypes in the vaccine. It is also approved for the prevention of otitis media caused by the seven serotypes covered by PCV7; however, no efficacy data for prevention of otitis media are available for the six additional serotypes.

Trends in invasive pneumococcal disease

Following the introduction of PCV7 in 2000, dramatic declines in invasive pneumococcal disease were reported among children aged <5 years as early as 2001. Before introduction of PCV7, rates of PC7-type invasive pneumococcal disease among children in this age were around 80 cases per 100,000 population. After the introduction of PCV7, rates of disease due to these 7 serotypes dropped dramatically to less than 1 case per 100,000 by 2007 (Figure 1).

The use of PCV7 also reduced the burden of invasive pneumococcal disease among older children and adults through reduced transmission of vaccine serotype pneumococci (herd protection). Declines in the incidence of PCV7-type invasive disease among adults were observed as early as 2001 and have continued since that time, reducing the incidence to 64–77% below the 1998–1999 baselines, depending on age.[18–20] Increases in disease caused by serotypes not included in PCV7 (i.e., replacement disease) are evident in children and certain adult populations with underlying illnesses but are small in magnitude compared with the overall reduction in disease.[21, 22] With the introduction of PCV13, it is anticipated that cases of invasive disease due to the 6 additional serotypes covered by the vaccine will decrease.

Figure 1. Penicillin resistance in *Streptococcus pneumoniae*, United States, 1979–2004



1979–1994: CDC Sentinel Surveillance System
1995–2004: CDC Active Bacterial Core Surveillance (ABCs) System, Emerging Infections Program[28]

Antimicrobial resistance trends

Before 1990, *S. pneumoniae* was almost uniformly susceptible to penicillin, allowing most physicians to treat persons with severe infections with penicillin alone. However, during the 1990's, resistance to penicillin and to multiple classes of antimicrobial agents spread rapidly in the United States with an increasing trend of invasive pneumococci resistant to 3 or more drug classes.[23–26]

Following the introduction of PCV7 into the routine childhood immunization program in 2000, the incidence of antibiotic-resistant invasive disease declined substantially among both young children and older persons.[20, 27–31] Between 1998–99 and 2008, penicillin-nonsusceptible IPD rates declined 64% for children aged <5 years and 45% for adults aged ≥65 years.[31] An increase in penicillin-nonsusceptible disease caused by serotypes not included in PCV7 was also identified during the same time period, although the magnitude of this effect remains small.[27] The prevalence of resistance varied by geographic area both before and after PCV7 introduction, with higher prevalence noted for the southeastern U.S.[23, 27] During 2007–08, serotypes unique to PCV13 (i.e., serotypes contained in PCV13 but not PCV7) caused 78–97% of penicillin-nonsusceptible IPD, depending on age.[31] With the introduction of PCV13 in 2010, further reductions in antibiotic-nonsusceptible IPD rates are anticipated.

In 2008, the Clinical and Laboratory Standards Institute (CLSI) established new, higher minimum inhibitory concentration (MIC) breakpoints for defining pneumococcal susceptibility to parenterally administered penicillin when treating non-meningitic pneumococcal disease.[32] Regardless of whether the old or new parenteral penicillin breakpoints are used, penicillin-nonsusceptible IPD caused by PCV7 serotypes has decreased significantly for all age groups and has almost disappeared except among adults aged ≥65 years. Under the new parenteral breakpoints, rates of penicillin-nonsusceptible IPD remain markedly below the rates that existed before PCV7 introduction for all age groups except adults aged 50–64 years.[31]

The emergence of drug resistant *S. pneumoniae* (DRSP) has made treatment of pneumococcal disease more difficult. Because of a lack of rapid, sensitive, and specific diagnostic tests, therapy for pneumonia and milder illnesses such as otitis media remains empiric. Groups of experts have provided national guidance for treating infections commonly caused by pneumococcus, such as otitis media and pneumonia, because of the increasing prevalence of DRSP.[33–36] Few communities exist in which resistance remains uncommon and even in these communities, resistant infections can occur. For these reasons, clinicians and public health officials should follow national guidelines rather than attempt to create local treatment recommendations based on local resistance data. Due to the limitations of current diagnostic testing, clinicians often prescribe empiric antibacterial therapy that is not indicated or is unnecessarily broad. Inappropriate antimicrobial use contributes to the development of DRSP. Principles have been developed to encourage appropriate use of antimicrobial agents for adults and children with upper respiratory infections.[6, 37–40]

III. Importance of Surveillance

Surveillance for invasive pneumococcal disease has four main goals:

- Characterization of national and local trends
- Detection of geographic and temporal changes in the prevalence of DRSP
- Monitoring impact of vaccines on disease
- Informing future vaccine development

With the recent introduction of PCV13, surveillance for invasive pneumococcal disease among children aged <5 years is particularly important for identifying populations that may not be receiving vaccination and for monitoring the incidence of disease caused by non-vaccine serotypes (i.e., replacement disease). Surveillance for invasive pneumococcal disease in persons ≥5 years is useful to monitor the impact of PPV vaccination, the indirect effects of PCV13, and replacement disease.

Serotyping of pneumococcal isolates can improve understanding of vaccine effects. However, serotyping is expensive and requires specialized reagents and extensive technical training; therefore, serotyping capacity is not widely available. The use of polymerase chain reaction (PCR) to identify pneumococcal capsular genes specific for individual capsular serotypes may be feasible for some state public health and academic research centers.[41, 42]

Pneumococcal surveillance enables recognition of new or rare resistance patterns. Surveillance information can be used on the national level for research and policy development and at the state or local level to raise awareness of DRSP among clinicians and the general public. Surveillance data also may be useful for tracking the impact of interventions aimed at reducing unnecessary use of antimicrobial agents.

IV. Disease Reduction Goals

Healthy People 2010 included targeted goals for reduction in invasive pneumococcal disease among children and adults as well as reduction in penicillin-resistant pneumococcal disease among children. Since the introduction of PCV7 into the childhood immunization schedule in 2000, a significant decrease in invasive pneumococcal disease among infants, children and adults has been observed.[20, 43] Among children aged <5 years, the incidence of invasive pneumococcal disease decreased by 74% between 1997 and 2008, from 77 to 22 new cases per 100,000 population, exceeding the 2010 target of 46 cases per 100,000.[44] Among adults aged ≥65 years, the incidence of invasive pneumococcal disease decreased by 34% between 1997 and 2008, from 62 to 41 new cases per 100,000 population, exceeding the 2010 target of 42 per 100,000. The incidence of penicillin-resistant pneumococcal infections among young children aged <5 years declined by 56% between 1997 and 2008, from 16 to 7 new cases per 100,000 moving toward the target of 6 cases per 100,000.[44]

Healthy People 2020 includes additional targets for reducing invasive pneumococcal disease in the coming years.[45] Target reduction goals for children aged <5 years and adults aged ≥65 years are 12 and 31 IPD cases per 100,000 respectively. In addition, Healthy People 2020 includes a target goal to decrease penicillin-resistant pneumococcal infections among children aged <5 years and adults aged ≥65 years to 3 and 2 cases per 100,000 respectively. Continuous surveillance is important to evaluate the impact of PCV13 on the incidence of invasive pneumococcal disease, antibiotic-resistant pneumococcal infections, and to monitor disease caused by pneumococcal serotypes not included in PCV13 (i.e., replacement disease).

Disease reduction goals also focus on minimizing complications of DRSP infections through prevention and control measures. Geographic differences in antibiotic prescribing practices have been described.[46] In sites where antibiotic prescribing is high, the proportion of nonsusceptible IPD is also high, suggesting that local prescribing practices may contribute to local resistance patterns.

In 1995, the CDC launched a national campaign to reduce antimicrobial resistance through promotion of appropriate antibiotic use. Initial efforts targeted the pediatric population and later expanded to adults. CDC surveys have shown that there is a perception among providers that patient expectations may encourage overuse of antibiotics. To overcome this, patient education resources were developed and are now available to aid in physician-patient communication (www.cdc.gov/getsmart). The program also works closely with a small number of state and local health departments to address appropriate antibiotic use in their communities. Formative research is currently underway to explore provider and patient knowledge and attitudes related to factors influencing antibiotic choices made by providers.

V. Case Definition

Case definitions for drug resistant *S. pneumoniae* (DRSP) and invasive pneumococcal disease were originally approved by the Council of State and Territorial Epidemiologists (CSTE) in 1994 and 2000, respectively.[47, 48] They were modified in 2006 to prevent duplicate reporting of individual cases.[49] The definition was further modified in 2009 to include all invasive

pneumococcal disease, regardless of drug resistance or the case patient's age. Beginning in 2010, the following definitions are in use for national reporting in the U.S.[50]

Confirmed: Isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid, or, less commonly, joint, pleural or pericardial fluid). (Event code 11723)

Suspected: The absence of the above criterion and either a medical record containing a diagnosis of invasive *Streptococcus pneumoniae* disease or death certificate listing invasive *S. pneumoniae* disease as the cause or a contributing cause of death.

Confirmed and suspected cases of invasive pneumococcal disease should be reported to public health authorities within one week of diagnosis. CSTE also recommends certain clinical and epidemiological information be collected, including date of illness onset, clinical syndrome (e.g., pneumonia, meningitis), underlying medical conditions, and pneumococcal vaccination history. DRSP is no longer collected in national surveillance as a separate event from invasive pneumococcal disease.[50]

VI. Laboratory Testing

Definitive diagnosis of pneumococcal infection is confirmed by the recovery of *S. pneumoniae* from a normally sterile body site (e.g., blood, CSF, pleural fluid, or peritoneal fluid). Because pneumococci frequently colonize the upper respiratory tract in the absence of disease, the clinical significance of recovering the organism from nonsterile body sites (e.g., expectorated sputum, conjunctiva) is less certain. Gram stain may be helpful in interpreting cultures of expectorated sputum; finding a predominance of gram-positive diplococci and >25 leukocytes with <10 epithelial cells per high power field on microscopic examination supports the diagnosis of pneumococcal pneumonia, but does not satisfy the case definition for national surveillance for invasive pneumococcal disease. Also, detection of pneumococcal capsular antigen in urine is useful for the diagnosis of pneumococcal pneumonia in adults.

Based on recommendations from the Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards, or NCCLS), clinical laboratories should test all isolates of *S. pneumoniae* from CSF for resistance to penicillin and cefotaxime, ceftriaxone, or meropenem, and vancomycin.[51] Penicillin susceptibility breakpoints were recently changed for nonmeningitis isolates, resulting in somewhat lower proportions of nonmeningeal isolates characterized as nonsusceptible.[52] For organisms from other sources, laboratories should consider testing for resistance to erythromycin, penicillin, trimethoprim-sulfamethoxazole, clindamycin, cefotaxime, ceftriaxone, meropenem, tetracycline, vancomycin, and a fluoroquinolone such as levofloxacin. Pneumococci resistant to vancomycin or linezolid have never been described. For vancomycin, a strain is considered non-susceptible if it has a minimum inhibitory concentration of >1 µg/ml or zone diameter <17 mm. For linezolid, nonsusceptible strains are those with a minimum inhibitory concentration of >2 µg/ml or zone diameter <21 mm. Strains found to be nonsusceptible to vancomycin or linezolid should be submitted to a reference laboratory for confirmatory testing, and if resistant, reported to the state health department.[51] Because pneumococci are fastidious organisms, some susceptibility testing methods used for other organisms are not appropriate for pneumococci (see the CLSI document for testing recommendations).[51]

Currently licensed vaccines target a limited number of pneumococcal polysaccharide capsule serotypes. Identifying the serotypes of pneumococcal strains can be useful for evaluating outbreaks of pneumococcal disease such as those that occur in institutional settings. Serotyping is currently performed in only a limited number of state public health laboratories, academic centers, or at the Centers for Disease Control and Prevention. CDC's Streptococcal Reference Laboratory will conduct serotyping of pneumococcal isolates from blood, CSF or other sterile sites in outbreak settings. State public health laboratories might consider adopting a PCR-based technique for determining capsular serotypes.[41, 42] CDC's Streptococcal Reference Laboratory provides numerous references and protocols for interested state public health laboratories which can be accessed at: http://www.cdc.gov/ncidod/biotech/strep/PCR.htm.

VII. Reporting

Each state and territory has regulations and laws governing the reporting of diseases and conditions of public health importance.[53] These regulations and laws list the diseases that are to be reported, and describe those persons or institutions responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Detailed information on reportable conditions in each state is available through the Council of State and Territorial Epidemiologists.[54]

Reporting to CDC

Most states currently require invasive pneumococcal disease to be reported to local or state health authorities, regardless of the age of the case or drug resistance. Additional states require reporting in limited populations, such as children <5 years of age. Confirmed and suspected cases of IPD should be reported to state or local health departments by clinicians, laboratories, hospitals, and pharmacies. Cases should be identified through microbiology laboratories, death certificates, hospital discharge or outpatient records, and electronic medical records. The following data are recommended for case investigation and reporting: patient's date of birth or age, the anatomic site of specimen collection, and type of infection. Other epidemiological information that is useful includes patient's gender, race and ethnicity, specimen collection date, whether the patient was hospitalized, clinical syndrome, antibiotic susceptibility, details of pneumococcal vaccination history, underlying medical conditions, daycare attendance, and outcome. Additional information may be collected at the direction of the state health department. The *S. pneumoniae* Surveillance Worksheet is included as Appendix 13. Confirmed cases of IPD should be reported using event code 11723 in the National Electronic Telecommunications System for Surveillance (NETSS).[50]

VIII. Vaccination

13-valent pneumococcal conjugate vaccine (PCV13)

The Advisory Committee on Immunization Practices (ACIP) recommends that the 13-valent pneumococcal conjugate vaccine (PCV13) be used for all children aged <5 years.[55] For routine immunization of infants, PCV13 is recommended as a 4-dose series at age 2, 4, 6, and 12–15 months.[1] Infants and children who have received ≥1 dose of PCV7 should complete the immunization series with PCV13. A single supplemental dose of PCV13 is recommended for all children aged 14–59 months who have received 4 doses of PCV7 or another age-appropriate, complete PCV7 schedule. For children who have underlying medical conditions, a supplemental PCV13 dose is recommended through age 71 months. Children aged 2–18 years with underlying medical conditions should also receive PPSV23 after completing all recommended doses of PCV13.

In addition, a single dose of PCV13 may be administered to children aged 6–18 years who are at increased risk for IPD because of sickle cell disease, human immunodeficiency virus (HIV) infection or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leaks, regardless of whether they have previously received PCV7 or PPSV23.[55] Routine use of PCV13 is not recommended for healthy children aged ≥5 years.

23-valent pneumococcal polysaccharide vaccine (PPV23)

PPV23 is approximately 56%–75% efficacious for the prevention of invasive pneumococcal infection caused by vaccine serotypes.[56, 57] Children aged ≥2 years with underlying medical conditions should receive PPV at least 8 weeks after completing all recommended doses of PCV131. A dose of PPV should be administered to all persons aged 5–64 years at increased risk of serious pneumococcal infection because of underlying medical conditions and to all persons ≥65 years of age.5

A single revaccination after at least 3–5 years (3 years if <10 years of age, 5 years if 10 or more years of age) should be considered for persons aged ≥2 to 64 years who are at highest risk or likely to have rapid declines in antibody levels. This includes those with functional or anatomic asplenia, HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma,

generalized malignancy, chronic renal failure, nephrotic syndrome or immunosuppression (e.g., organ transplants or receiving chemotherapy). Previously vaccinated persons should be revaccinated at 65 years of age or older, providing at least 5 years has passed since the first dose. Pneumococcal vaccine may be administered concurrently with influenza vaccine by separate injection in the opposite arm.

IX. Enhancing Surveillance

Several surveillance activities may improve the detection and reporting of pneumococcal disease and the quality of the reports.

Establishing reporting of all invasive pneumococcal disease in young children

CSTE has recommended reporting of all invasive pneumococcal disease in children aged <5 years to monitor the impact of the pneumococcal conjugate vaccine for this age group; to track progress toward Healthy People 2020 objectives; to monitor drug resistance among pneumococci, and; to assist public health jurisdictions in raising awareness of vaccine recommendations.

Enhancing reporting of Antibiotic Susceptibility Results

Concern over rising resistance to antibiotics has prompted many state health departments to increase their focus on reporting susceptibility results. CDC has worked with state health departments to evaluate different surveillance methods to determine which methods would enhance the reliability of surveillance data, given certain goals and resource limitations.[58] Use of aggregated antibiogram data collected from all hospital laboratories in an area has been shown to give a relatively accurate description of the proportion of isolates that are resistant to penicillin and a limited number of other drugs,[59] but such data typically cannot be analyzed by age group or other factors of interest. Sentinel systems, which may collect individual reports with more details from a limited number of laboratories, can give an accurate view of resistance if designed well.[60]

Encouraging provider reporting

Most states' infectious disease surveillance systems depend upon the receipt of case reports from health-care providers and laboratories. These data are often incomplete and may not be representative of certain populations; completeness of reporting has been estimated to vary from 6% to 90% for many of the common notifiable diseases.[53] Therefore, it is important to educate providers about which events should be reported, and about how accurate reporting is critical to control of communicable diseases. Increasing provider awareness of local rates of IPD and local reporting requirements may enhance surveillance.

Improving detection of DRSP in laboratories by promoting optimal techniques and appropriate interpretive standards

Because pneumococci are fastidious organisms, laboratory methods that are appropriate for some organisms are not appropriate for pneumococci.[61] In addition, many laboratories are not monitoring resistance to some agents that are widely used for suspected pneumococcal infections, such as fluoroquinolone agents.[24] Universal adoption of optimal testing methods and testing for resistance to recommended antibiotics would improve our ability to detect and monitor resistant pathogens.

Streamlining reporting using electronic methods

Many surveillance systems still rely on paper and pencil for data collection; use of electronic data transferred directly from clinical laboratories significantly improves reporting speed and data quality as well as reduces workload. Efforts are underway to implement electronic reporting, including the creation of a CSTE/CDC Joint Electronic Laboratory Reporting Taskforce.[62]

X. Case Investigations

As with most respiratory pathogens, rapid, sensitive, and specific diagnostic tests are not available; thus, early in the course of illness, diagnosis of *S. pneumoniae* infection is usually presumptive and the choice of antimicrobial therapy is nearly always empiric. However, once *S. pneumoniae* is isolated from a normally sterile body site, antimicrobial susceptibility testing may be necessary for patient management. Case investigations are not usually warranted, except in outbreaks or as determined by the state health department. CDC is available during outbreaks to assist with epidemiologic and laboratory investigations.

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