



Improving the Diagnosis, Management, and Treatment of Infectious Conjunctivitis

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September 28, 2010

I have financial interest in ...

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Rapid Pathogen Screening
Science Based Health
TearLab
Topcon
TruVision Systems
VMax

Evidence Based Goals

- Point-of-care diagnostic tests improve clinical accuracy
- Acute infectious conjunctivitis
 - Epidemiology
 - Diagnosis
 - Treatment
- Misdiagnosis leads to mistreatment
- Morbidity associated with adenoviral conjunctivitis
- Cost effectiveness of diagnostic testing for conjunctivitis

Common POC Tests

Examples of commonly performed office tests

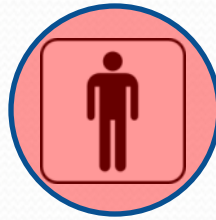
- Streptococcus A
- Influenza A/B
- Mononucleosis

Why Perform POC Tests?

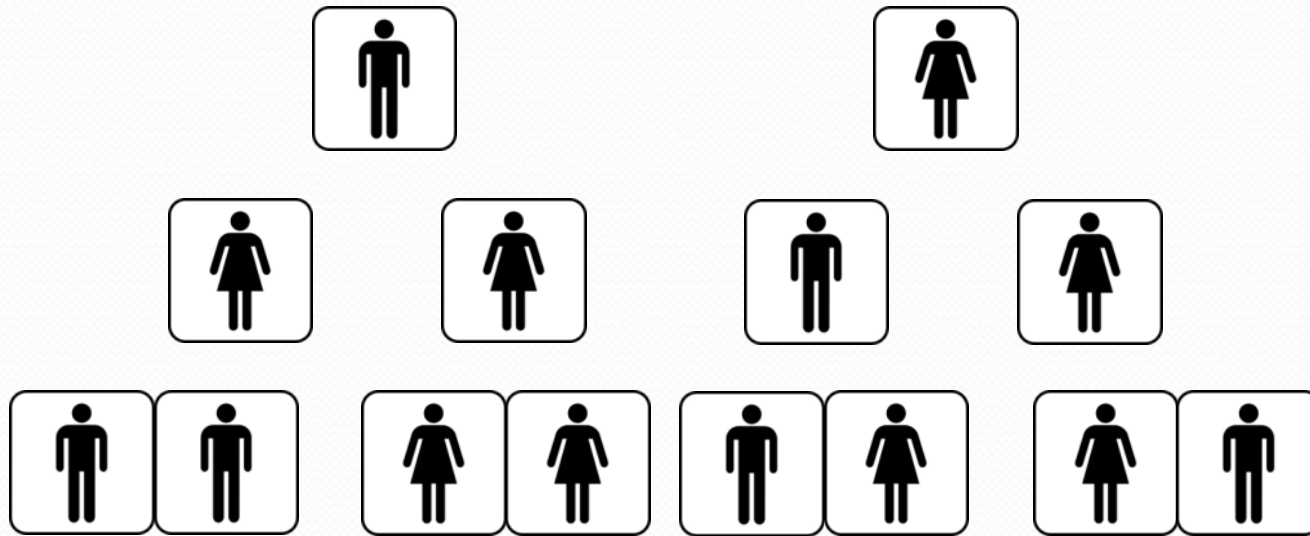
- Patients want a definitive diagnosis
- Rapid results to prevent misdiagnosis and unnecessary empiric treatments
- Prevent additional spread of disease

Why Does A Correct Adenoviral Diagnosis Matter?

Reduce spread of disease!



Reduce morbidity!



Reduce costs!

Win-Win-Win Opportunity

Patients

Definitive diagnosis

Avoid unnecessary treatments and adverse events

Contagious precautions to limit disease spread

Personal cost savings

Clinicians

Reduce clinical diagnostic uncertainty

Limit medical-legal risk exposure

Best practices – Limit absenteeism

Society

Limit absenteeism to school, work, daycare

Reduce costs on revisits, complications

Acute Conjunctivitis

- Most common cause of a “red eye”
- Most often caused by a bacteria, virus or allergen
- 95-99% of non-eye doctors prescribe antibiotics for all cases of conjunctivitis ¹⁻²

**In the US, there are approximately
6 million cases of conjunctivitis annually**

Acute Infectious Conjunctivitis

- 40-60% is bacterial conjunctivitis³⁻¹⁴
 - More common in children
 - Hyperacute case...think Gonococcal
 - 1-2% Chlamydia...becomes chronic⁹
- 20-70% is viral conjunctivitis³⁻¹⁴
 - 65-90% is caused by adenovirus¹¹⁻¹⁴
 - 3-5% HSV^{11,13,15}
 - Other viruses combine for less than 10% including: CMV, Influenza, EBV, Enterovirus and Coxsackie

Bacterial Conjunctivitis

- More common in children and young adults
- Most commonly caused by:
 - Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis
- Children <5 years old usually have Streptococcus pneumoniae
- Adults – Typically caused by Staphylococcus aureus

Bacterial Conjunctivitis

- Spread by direct contact with the patient and his or her secretions or with contaminated objects and surfaces
- Usually less contagious than viral but can be highly contagious
 - Unencapsulated strains of *S. pneumoniae* have shown attack rates as high as 14%

Bacterial Conjunctivitis

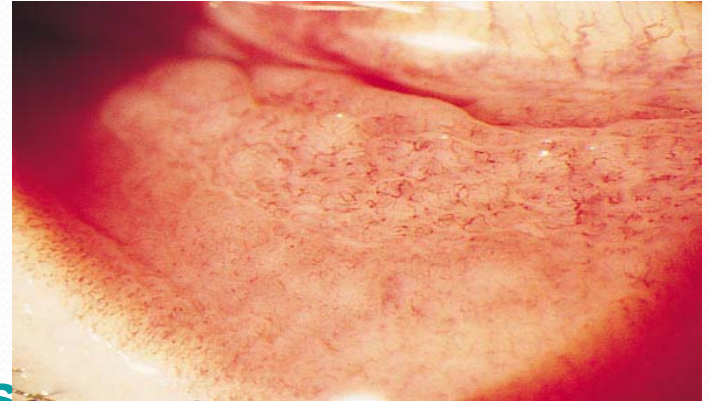
- **Hyperacute Conjunctivitis**
 - *Neisseria gonorrhoea*
 - Profuse, rapidly progressive, copious purulent discharge
 - Signs include marked chemosis, lid swelling, and tender preauricular adenopathy
 - Keratitis and perforation can occur
 - Sexually active
 - Transmitted from the genitalia to the hands and then to the eyes; urethritis is typically present



Bacterial Conjunctivitis

Chlamydial Infections

- **Trachoma** — Limited to underdeveloped regions
- **Adult inclusion conjunctivitis**
 - not strictly an acute conjunctivitis, but rather a chronic, indolent conjunctivitis
 - It is a sexually transmitted infection caused by certain serotypes of *Chlamydia trachomatis* (D-K)
 - Concurrent asymptomatic urogenital infection is typically present in up to 70% of cases



Bacterial Conjunctivitis

Chlamydial Infections

- Unilateral > Bilateral
- Superior pannus
- + Lymphadenopathy
- Follicular conjunctivitis of weeks to months duration that has not responded to topical antibiotic therapy
- May be associated with a keratitis
- Peripheral Subepithelial infiltrates

Adenoviral Conjunctivitis

- Human adenoviruses are classified into six subgenera and 53 serotypes
- One-third of serotypes can cause conjunctivitis but the most common are related to the following serotypes:

NFC	1-11,14-17,19,20,22,26
PCF	1,3,4,7,11,14,16,19,37
AHC	8,11,14, 19,37
EKC	3,4,7,8,10,11,19,21,37

Adenoviral Conjunctivitis

	Epidemic Keratoconjunctivitis (EKC)	Pharyngealconjunctival Fever (PCF)	Acute Nonspecific Follicular Conjunctivitis
Serotypes	8, 19 and 37	3, 4, 5 and 7	1–11, 19 and others
Symptoms	Tearing, photophobia, FB sensation, pain, blepharospasm, blurred vision	Slight itching, burning, tearing, little photophobia, FB sensation <u>Systemic:</u> Myalgia, Malaise, GI Disturbances, Fever, Pharyngitis	Photophobia, tearing, blurred vision Recent Cold or Flu by Hx
Signs	Chemosis Severe diffuse bulb/palp. Inject Subconj heme Lid edema Mixedpapill/follic.Rxn Pseudomembrane SPK, SEI Iritis Palpable Tender PAN	Chemosis Mod. diffuse bulb/palp.Injection Follicular reaction Lid edema Eyelid crusting Lid tenderness SPK, SEI Palpable Tender PAN	Chemosis Mild injection Mild lid edema Variable follicular Rxn **Cornea rarely involved Palpable non-tender PAN

Adenoviral Conjunctivitis

Epidemic Keratoconjunctivitis (EKC)	Pharyngealconjunctival Fever (PCF)	Acute Nonspecific Follicular Conjunctivitis
Bilateral	Assymetric Bilateral	Assymetric Bilateral
Extremely contagious	Highly contagious	Moderately contagious
Duration: 2 – 5 weeks	Duration: 7 – 14 days	Duration: 3 – 7 days
More common in young children and adults	Usually seen in children and families	No age predilection
Spring and Summer	Summer > Winter	All seasons

Adenoviral Conjunctivitis

- Adenoviral conjunctivitis is the most common form of viral conjunctivitis
- Usually self limiting but 30-50% of EKC and 5% of PCF can cause complications²²⁻²⁹
- May be associated with significant ocular morbidity and socioeconomic problems due to missed work or school
- Generally regarded as the most common ocular surface viral infection worldwide

Adenovirus Transmission

- Can live on inanimate surfaces for 4-5 weeks ^{31,32}
- Attack rates from 10-50% ³⁴⁻⁴¹
- Stable to adverse chemical and physical conditions
- Can shed for 14-16 days after initial symptoms (**contagious!**)^{42,43}
- Common modes of transmission:
 - Hand-to-eye
 - Airborne respiratory droplets



Acute Red Eye

Primary Differential Diagnosis:

Conjunctivitis

- Allergic
- Viral
- Bacterial
 - Acute – Staph, Strep, Hemophilus, Moraxella
 - Hyperacute - Gonorrhea
 - Chlamydia

Molluscum Contagiosum

Contact Lens Related (Over-wear Syndrome)

Blepharitis /Dry Eyes

Episcleritis

Medication

Glaucoma



Key History & Signs

History

- SCL use
- URI
- Sick contacts
- Recurrence pattern
- Unilateral vs. Bilateral
- Temporal spread



Key History & Signs

Signs

- Lymphadenopathy
- Follicles
- Discharge



Clinical Diagnosis

What we were taught...

Most likely viral if:

- Starts in one eye and spreads to the other
- Associated with watery discharge
- Associated with URI or sick contacts
- + Preauricular lymph node

Most likely bacterial if:

- Often unilateral but can be bilateral
- Purulent discharge
- No Lymphadenopathy
- Associated with ear infection in small children

Clinical Diagnosis

What the literature tells us...

PRESENTATIONS	VIRAL	BACTERIAL
Bilateral Disease	35%	50% - 74%
Upper Respiratory Infection	55%	5% - 8%
Otitis Media	10%	8% - 33%

Gigliotti F, Williams WT, Hayden FG, Hendley JO. Etiology of acute conjunctivitis in children. *J Pediatr.* 1981;98:531-6.

Fitch CP, Rapoza PA, Owens S, Murillo-Lopez F, Johnson RA, Quinn TC, Pepose JS, Taylor HR. Epidemiology and diagnosis of acute conjunctivitis at inner-city hospital. *Ophthalmology.* 1989;96:1215-20.

Clinical Diagnosis

What the literature tells us...

PHYSICAL SIGNS	VIRAL	BACTERIAL
Follicles	47%	42%
Superficial Punctate Keratopathy	13%	11%
+ Pre-auricular Lymphadenopathy	31%	6%
Bulbar Injection	100%	94%

Fitch CP, Rapoza PA, Owens S, Murillo-Lopez F, Johnson RA, Quinn TC, Pepose JS, Taylor HR. Epidemiology and diagnosis of acute conjunctivitis at inner-city hospital. *Ophthalmology*. 1989;96:1215-20.

Bacterial Conjunctivitis

Lymphadenopathy

- Moraxella catarrhalis
- MRSA
- Chlamydia
- Neisseria gonorrhoea

Clinical Diagnosis

What the literature tells us...

SYMPTOMS	VIRAL	BACTERIAL
Redness	81%	83%
Itching	38%	33%
Burning	31%	11%
Foreign Body Sensation	44%	6%
Photophobia	38%	22%
Irritation	19%	17%

Gigliotti F, Williams WT, Hayden FG, Hendley JO. Etiology of acute conjunctivitis in children. *J Pediatr.* 1981;98:531-6.

Fitch CP, Rapoza PA, Owens S, Murillo-Lopez F, Johnson RA, Quinn TC, Pepose JS, Taylor HR. Epidemiology and diagnosis of acute conjunctivitis at inner-city hospital. *Ophthalmology.* 1989;96:1215-20.

Acute Conjunctivitis

SYMPTOMS	VIRAL	BACTERIAL
Watery Discharge	50%	39%
Mucoid Discharge	19%	17%
Purulence	25%	28%

Fitch CP, Rapoza PA, Owens S, Murillo-Lopez F, Johnson RA, Quinn TC, Pepose JS, Taylor HR. Epidemiology and diagnosis of acute conjunctivitis at inner-city hospital. *Ophthalmology*. 1989;96:1215-20.

Purulent Discharge	45%	83% - 93%
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Gigliotti F, Williams WT, Hayden FG, Hendley JO. Etiology of acute conjunctivitis in children. *J Pediatr*. 1981;98:531-6.

Clinical Accuracy

No evidence exists to support the diagnostic usefulness of clinical signs, symptoms, or both in distinguishing bacterial conjunctivitis from viral conjunctivitis.

Rietveld RP, van Weert HC, ter Riet G, Bindels PJ. Diagnostic impact of signs and symptoms in acute infectious conjunctivitis: systematic literature search. *BMJ*. 2003 Oct 4;327(7418):789.

Clinical Accuracy

- Diagnosis based on history and clinical exam
 - Misdiagnosis ~50% of all cases ^{7,9,16-19}
- No routine testing conducted (expensive, time consuming)

**“If antibiotics are ineffective,
it must be viral...”**

Clinical Accuracy

- Leibowitz et al. – Only 31% of presumed bacterial conjunctivitis were culture positive whereas 52% with presumed viral conjunctivitis were culture positive for pathogenic bacteria¹⁶
- Cheung et al. – 67% of adenoviral cases presented unilaterally and the misdiagnosis rate was 42% in these patients¹⁷
- During a clinical trial to evaluate cidofovir treatment at 16 academic centers, experts showed a clinical accuracy of about 48%¹⁸

Clinical Accuracy

Eyes "stuck shut" in the morning

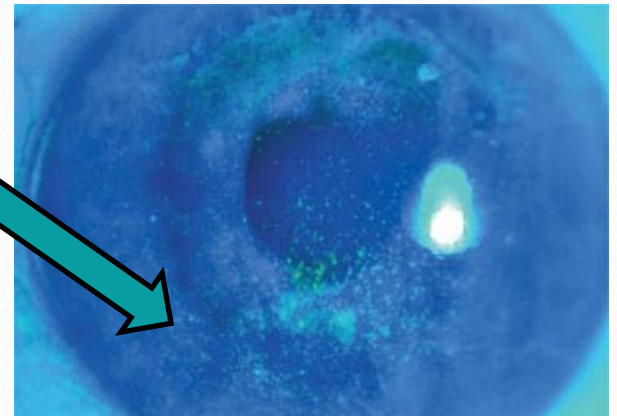
In a cohort of 184 adults with a red eye and either an eye stuck shut in the morning or purulent or mucopurulent discharge:

- Among 57 confirmed patients with bacterial conjunctivitis, **53%** had one eye stuck shut and **39%** had two eyes stuck shut
- Among 120 patients without bacterial conjunctivitis, **62%** had one eye stuck shut and **11%** had two eyes stuck shut

Adenoviral Morbidity

Occurs in 30-50% of EKC and 5% of PCF...²²⁻²⁹

- Persistent tear insufficiency for up to 30 days post-infection ²⁸
- Conjunctival scarring with goblet cell loss and permanent dry eyes ²⁷
- Symblepharon ²⁷



Adenoviral Morbidity

Occurs in 30-50% of EKC and 5% of PCF...²²⁻²⁹

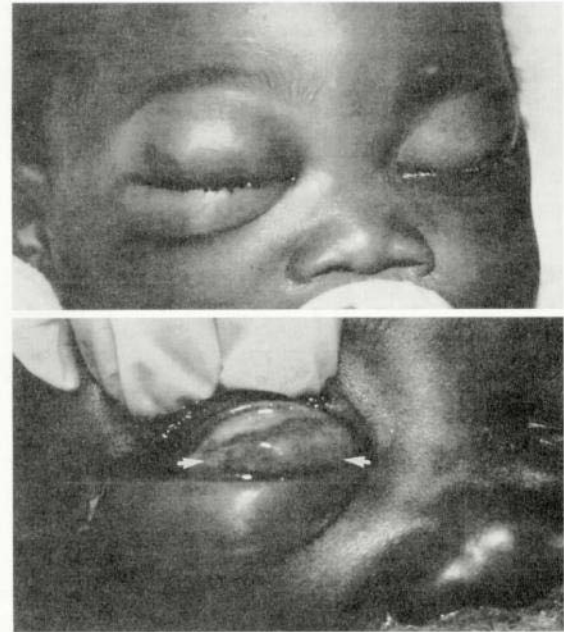
- Lacrimal drainage problems ²⁹
- Subepithelial Infiltrates (SEIs) ²²
 - Vision loss
 - Light sensitivity
 - May have return of symptoms post taper (months–years)
 - Requires long term steroid treatment



Diagnostic Challenges

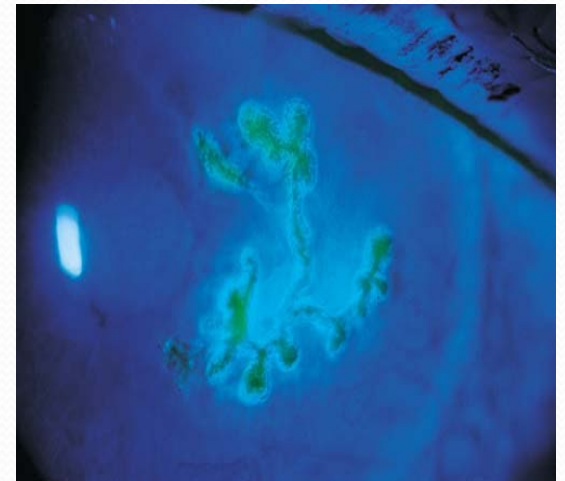
In children, adenoviral infections can mimic preseptal and orbital cellulitis

Ruttum et al revealed that 16% (13/80) of patients with signs of preseptal or orbital infection were culture positive for adenovirus



HSV Conjunctivitis

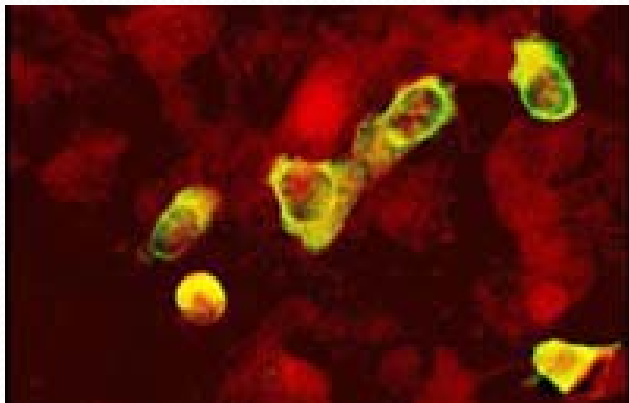
- Incidence = 3-5% of all acute viral conjunctivitis⁴⁴⁻⁴⁶
- Unilateral >> Bilateral
- Pain, injection, photophobia
- Skin vesicles
- (+) Follicles
- (+) Pre-auricular node
- Medical - Legal



Traditional Lab Testing Options

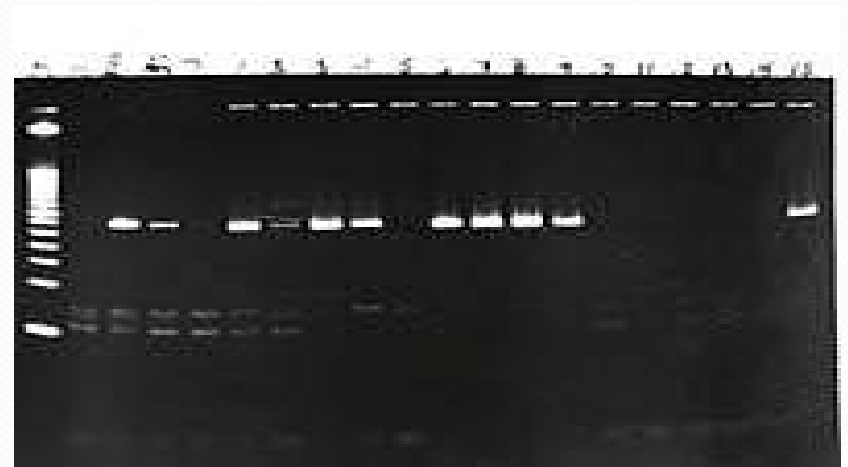
Cell Cultures²⁰⁻²¹

- 3-21 days for results, not point-of-care
- “Gold Standard”
- Requires empiric treatment until results are known



PCR²⁰⁻²¹

- 1-3 days for results, not point-of-care
- Expensive
- Requires technical expertise



POC Test Now Available

- RPS Adeno Detector™
- Detects presence of adenovirus in red eye
- CLIA-waived



RPS Adeno Detector™ Accuracy

- Prospective, masked, multi-center clinical trial in US and Europe ⁵
- 186 consecutive patients
- Examined all cases of acute conjunctivitis
- Compared to both cell culture and PCR
- 25% of all acute conjunctivitis confirmed as adenovirus



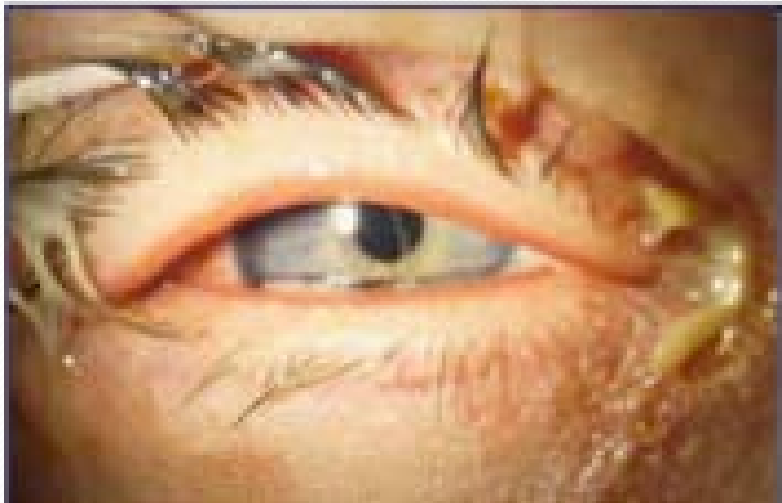
RPS Adeno Detector™ Accuracy

	Adeno Detector	Cell Culture
Sensitivity	89%	91%*
Specificity	94%	100%

*Culture is not 100% sensitive because 4 cases were found positive by both PCR and the RPS Adeno Detector

Four Step Testing Process

A patient presents with Acute Conjunctivitis with a discharge.



STEP 1. Use Sample Collector to collect a concentrated sample of the adenovirus in tear fluid from the conjunctiva.

Four Step Testing Process

STEP 2. Transfer sample to the test strip.



STEP 3. Dip test cassette into buffer solution for 15 seconds.



STEP 4. In less than 10 minutes read test results.



RPS Adeno Detector showing **POSITIVE** results for adenovirus (2 red lines)

Clinical Guidelines Support

- American Academy of Ophthalmology: Preferred Practice Patterns, 2008
- American Academy of Pediatrics: Red Book, 2009
- American College of Physicians: PIER, 2006

AAO Preferred Practice Patterns

Viral Diagnostic Tests

“Viral cultures are not routinely used to establish a diagnosis. A rapid, in-office immunodiagnostic test using antigen detection is available for adenovirus conjunctivitis. In a study of 186 patients with acute conjunctivitis, this test had a sensitivity of 88% to 89% and a specificity of 91% to 94%. Immunodiagnostic tests may be available for other viruses, but these are not validated for ocular specimens. Polymerase chain reaction (PCR) may be used to detect viral deoxyribonucleic acid. Availability will vary depending on laboratory policy.”

Red Book Clinical Guidelines

“The preferred methods for diagnosis of adenovirus infection include cell culture as well as antigen and DNA detection. Adenovirus antigens can be detected in less than 30 minutes in a variety of body fluids from infected people ... These rapid assays especially are useful for diagnosis of diarrheal disease, because enteric adenovirus types 40 and 41 usually cannot be isolated in standard cell cultures, and for ocular disease.”

Red Book 2009

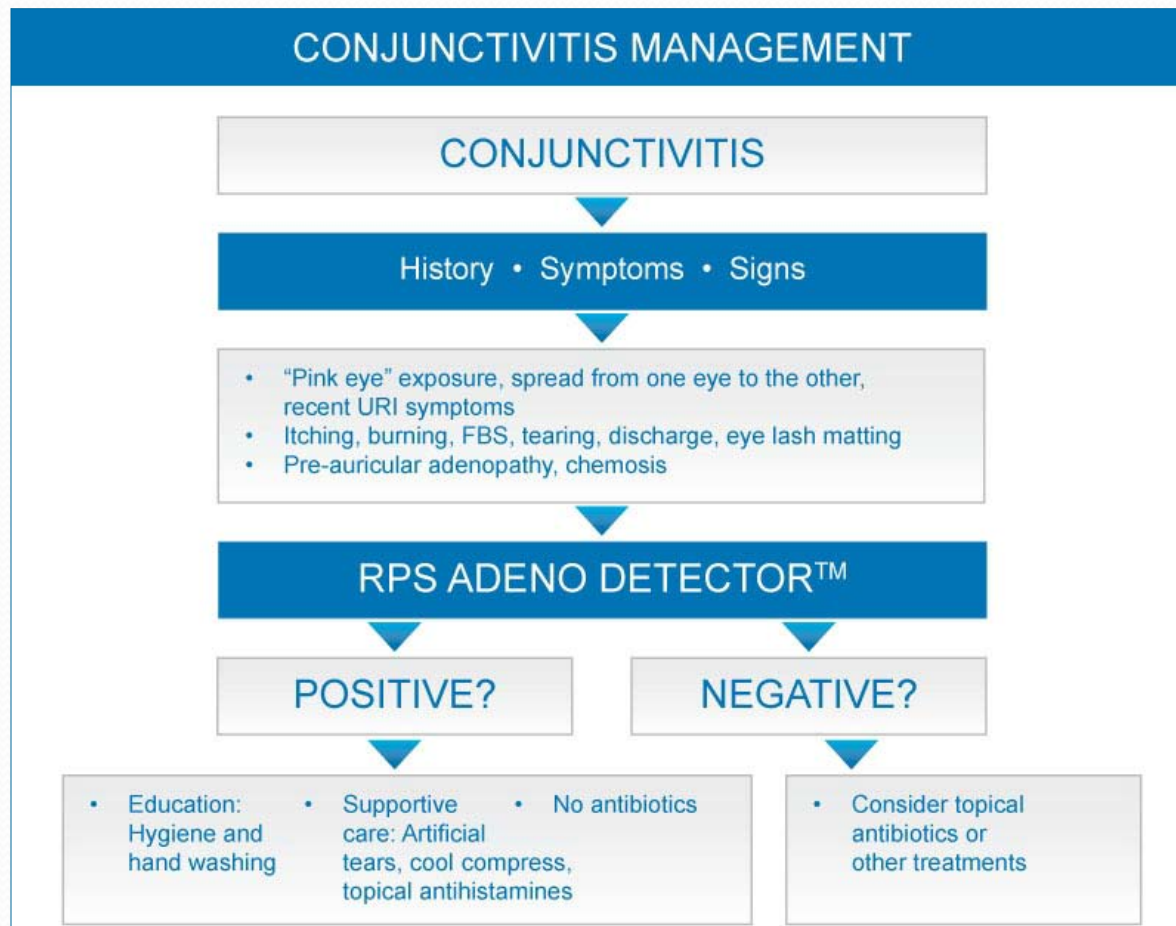
PIER Clinical Guidelines

Rationale:

“Although most conjunctivitis can be diagnosed on history and physical examination as infectious, the nature of the infectious agent, a virus or bacteria, is often difficult to determine. In-office testing for adenovirus may assist in establishing a correct diagnosis, but in some unusual cases and in patients unresponsive to treatment, special tests may be indicated.”

Red Book 2009

Acute Conjunctivitis Management



Sambursky R, Tauber S, Schirra F, et al. The RPS adeno detector for diagnosing adenoviral conjunctivitis. *Ophthalmology*. 2006;113:1758-64.

Treatment Strategy for Bacterial Conjunctivitis

According to Rose et al (2005), patients with bacterial conjunctivitis get better without treatment....So why treat patients?

1. Reduce duration of disease by 1-2 days
2. Make the patient symptomatically feel better
3. Reduce the contagious risk, especially if returning to work, school, daycare

Issues with treatment to consider...

- Medication cost to patient
 - Medication toxicity and allergy profile
 - Antimicrobial resistance
 - Dosing regimen and comfort of drops → influence compliance
5. Medical legal risks

Treatment for Bacterial Conjunctivitis

Selecting the Right Antibiotic

- **Cheap:** Gentamycin, Tobramycin, Sulfa, Erythromycin, Neomycin, Bacitracin
- **Expensive:** Fluoroquinolones, Zylet, Tobradex
- **Resistance:** Up to 25-50% for Aminoglycosides, Erythromycin, and 3rd generation Fluoroquinolones; lower rates for Azithromycin; lowest for 4th generation Fluoroquinolones
- **Toxicity:** Up to 16% Aminoglycosides
- **Allergies:** 10-20% Sulfa, Neomycin, Bacitracin
- **Comfort:** Fluoroquinolones most comfortable; Sulfa with increased stinging
- **Dosing:** Azithromycin only BID x 2 days then QD

Bacterial Conjunctivitis Treatment

- **Neisseria Gonorrhoea**

- Ceftriaxone 1g intramuscularly in a single dose
- If corneal involvement exists, treat with ceftriaxone 1g intravenously every 12-24 hours
- Topical fluoroquinolone q1h
- Saline irrigation until the discharge resolves
- Treat for possible Chlamydial co-infection

- **Chlamydia**

- Azithromycin 1g PO single dose or doxycycline 100mg po BID x 7 days
- Topical Azithromycin or Erythromycin ointment BID to TID for 2-3 weeks

Adenoviral Conjunctivitis Treatment

- Artificial tears (Preservative Free – may refrigerate)
- Cool compresses
- Antihistamine for severe itching (3-4 days only)
- Hand washing
- Decontamination at home

NO ANTIBIOTICS REQUIRED!

Treatment for Adenoviral Conjunctivitis

- Currently there are no available FDA-cleared drugs with labeling specific to the treatment of adenoviral conjunctivitis
- During the 2009 American Academy of Ophthalmology, a panel discussion centered on the promising results of off-label applications for some currently available drug therapies
- Several drugs are currently in clinical trials, with projected launch dates in the next 3 years

Reducing Spread of Adenoviral Disease

- Keep out of work/school (~1 week)
- Personal hygiene
- Hand-washing!
 - 46% of patients with adenoviral disease had adenovirus cultured from hands³³
- Replace contact lenses and cases, make-up

Secondary and Co-infections

- Co-infections in 1-2% - ? normal flora⁶
- Secondary infections are rare in immunocompetent patients
- Viral infection is the rate limiting step to healing
7-28 days vs. 3-7 days
- Rose et al. showed patients in a large multicenter RCT with bacterial conjunctivitis improve spontaneously without need for antibiotics – antibiotics only reduces duration by 1-2 days⁵²

Secondary and Co-Infections

- Consider antibiotics in presumed viral conjunctivitis if ...
- Immunocompromised patients
- Contact lens patients

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Problems with Steroid Treatment

Although it may make the patient feel better...

- Risk of HSV (~3-21% of pink eye)⁴⁶⁻⁴⁷
- Increase infectivity and viral replication of adenovirus⁴⁸⁻⁵¹
- Prolongation of adenoviral positive cultures⁴⁸⁻⁵¹
- Result: increase potential spread of adenovirus⁴⁸⁻⁵¹
- Medical-Legal Issues

Cost Effectiveness

RPS Adeno Detector™

- Savings of \$430 million nationally ³⁰
- Over 1 million cases of inappropriate antibiotics could be avoided ³⁰



Reimbursement

- CPT Code 87809QW
- Medicare Reimbursement \$17.11
- Device end user price ~\$12 (available direct and through distribution)

RPS Adeno Detector™ Benefits

- Aids clinicians to make accurate diagnoses and institute appropriate treatment
- Limits empirical treatments – reduces unnecessary prescriptions of antibiotics and their associated side effects
- Fosters patient acceptance of more supportive care
- Limits spread of disease

Key Points

- Adenovirus is extremely contagious and can lead to significant ocular morbidity
- Studies show that it is clinically challenging to differentiate viral from bacterial conjunctivitis and impossible to determine who is contagious
- In-office rapid immunoassays can aid in confirming a diagnosis of adenoviral conjunctivitis

Key Points

- Prophylactic antibiotics against secondary bacterial infections are unnecessary for cases of presumed viral conjunctivitis
- Unnecessary antibiotics contribute to antibiotic resistance, toxicities, allergies and healthcare costs



Questions?



Thank You

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