THE SCIENCE OF ABHR PERFORMANCE

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Agenda

- Hand Hygiene Overview
- Use of Alcohol for Skin Disinfection
- Methods to Evaluate ABHR Efficacy
- Achieving Clinical Benefit with ABHR
  - Factors Influencing ABHR Efficacy
  - Factors Influencing Hand Hygiene Compliance
- Conclusion

Hands Are the Most Common Means of Microbial Spread

Acquisition of MRSA on hands after touching the bedrail of a colonized patient

Acquisition of MRSA on hands after examination of a colonized patient

“Hand Hygiene is the single most important procedure for preventing the transfer of microorganisms and therefore preventing the incidence of diseases”

Use of Alcohol for Skin Disinfection

Alcohol as an Antiseptic

- Robert Koch: Conducted first systematic in vitro studies of ethyl alcohol against pure cultures of bacteria (1880s)
- Philip Price demonstrated that alcohol highly effective for skin antisepsis (1930s to 1950)
- Peter Kalmar developed the first commercial ABHR (1965)
- Manfred Rotter developed European methods for measuring efficacy of alcohol based surgical and hygienic handrubs (1970s to 1980s)

Log Reduction Tutorial

<table>
<thead>
<tr>
<th>Log Reduction</th>
<th>Percent Reduction of Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>99%</td>
</tr>
<tr>
<td>3</td>
<td>99.9%</td>
</tr>
<tr>
<td>4</td>
<td>99.99%</td>
</tr>
<tr>
<td>5</td>
<td>99.999%</td>
</tr>
</tbody>
</table>

Example: Start with 1 million bacteria
- 1 log reduction: 900,000 are killed and 100,000 remain
- 2 log reduction: 990,000 are killed and 10,000 remain
- 3 log reduction: 999,000 are killed and 1,000 remain
Alcohol Efficacy: Time-Kill Dose Response

- There is a "threshold" concentration when alcohol becomes bactericidal
- 4 log₁₀ reduction is achieved with 40% for Gram-negative bacteria and 50% for Gram-positive bacteria
- Activity does not improve above this level

How does alcohol kill bacteria?

- Damages cell membrane → loss of cell integrity
- Inactivates proteins ("denatures")
- Acts and evaporates very rapidly
- Not associated with resistance development

Skin Antiseptic Activity of Short-Chain Alcohols

- Alcohol-in-water mixtures tested
  - 1 minute contact time
- All 3 alcohols were highly effective
- U.S. Regulations:
  - n-propanol not allowed (without NDA)

Efficacy depends... “not only on the concentration but also on the type of alcohol used”
Resident and Transient Flora

- Resident microflora: Normal inhabitants of the skin:
  - Colonize deeper layers of the skin
  - Difficult to remove
  - Target for pre-surgical hand scrubs/rubs

- Transient microflora: Visitors to the skin, picked up from environment:
  - On superficial layers of skin
  - Easier to remove
  - Target for alcohol-based hand rubs

Alcohol-Based Handrubs Kill Transient Bacteria Effectively

A "clean" hand experimentally contaminated with *E. coli*.

Blue = *E. coli*

White = Resident microflora

Experimentally contaminated hand (other hand) after using alcohol-based hand rub

*E. coli* eliminated, revealing the resident microflora

Result - Effective *E. coli* kill; resident bacteria remain

Alcohol and Viruses

- Highly active against enveloped viruses
- Activity against non-enveloped viruses depends on alcohol type, concentration, and specific virus
- Formulation can influence activity
- Norovirus:
  - Cannot be grown in culture
  - More research and better test methods needed!

During outbreaks, use soap and water for hand hygiene after providing care or having contact with patients suspected or confirmed with norovirus gastroenteritis.

Alcohol and *Clostridium difficile*

- Alcohol does not kill *C. difficile* spores.\(^1\)
- Handwashing is more efficacious than ABHR but not optimum.\(^2,3\)
- Preferentially perform hand hygiene with soap and water after caring for a patient with CDI only during outbreaks.\(^4\)

"...there have been no studies in acute care settings that have demonstrated an increase in CDI with alcohol-based hand hygiene products or a decrease in CDI with soap and water."\(^*\)


Methodologies for evaluating the efficacy of alcohol-based hand rubs

- Safe and effective active ingredients
- Use concentrations
- Dosage forms
- Labeling
- Efficacy testing

Over-the-Counter Drug Monograph System

A drug monograph establishes conditions under which an OTC drug is GRASE (Generally Recognized as Safe and Effective)
FDA Efficacy Testing Requirements (Overview)

**in vitro**
(Time-Kill)

+ 

**in vivo**
(HCPHW)*

*Healthcare Personnel Handwash (HCPHW)*

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“Time-Kill”

- **in vitro** assay
  - ASTM E2783-10
- Measures rapid bactericidal (killing) action of products
- Can test almost any microorganism by this method

*In vitro* results do not predict antimicrobial performance on hands.

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Healthcare Personnel Handwash (HCPHW)

- Based on ASTM E1174
- Predicts the reduction of organisms by washing or sanitizing hands after handling contaminated objects
- Measures reduction of transient organisms after single or multiple product uses

**FDA Endpoints:**

- Bacterial Reduction (log10)
  - 1st Application: 2 log
  - 10th Application: 3 log

Comparison of *In vivo* Test Methods

**Healthcare Personnel Handwash**
- Challenge organism: *S. marcescens*
- Product evaluated at single and multiple uses

**EN1500: Hygienic Hand Rub**
- Challenge organism: *E. coli*
- Single product cross-over design
- Must show non-inferiority to internal reference

Expert Opinions on Hand Hygiene Test Methods

"New Methods For The Future"...


Summary and Conclusions

- Hand Hygiene is the single most important intervention to help reduce the spread of HAI
- ABHRs are critical to help reduce the spread of healthcare-associated infections
- It is important to understand ABHR test methods when evaluating and interpreting product claims
  - Data from *in vivo* methods is essential to differentiate ABHR efficacy
  - Be cautious of "99.99999999999% game"
- There is still opportunity for improvement of hand hygiene technology and test methods
Achieving Clinical Benefit With Alcohol-Based Handrubs

Achieving Clinical Benefit with ABHRs: Whole Systems Model

Factors Influencing ABHR Antimicrobial Efficacy:
Concentration Dependence of the Activity of Short-Chain Alcohols

- Test substances:
  - Alcohol-in-water mixtures
- Test Method = EN1500
  - 1 minute contact time

**EFFICACY OF ALCOHOL-IN WATER SOLUTIONS INFLUENCED BY ALCOHOL CONCENTRATIONS.**


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Influence of ABHR Formulation

- ABHR formulations often contain:
  - Alcohol — Buffering Systems
  - Water — Secondary Actives
  - Thickeners — Surfactants
  - Moisturizers
- Ingredients create specific attributes:
  - Skin tolerance, skin moisturization, aesthetic properties (e.g., skin feel, fragrance)
  - Enable specific delivery formats (rinse, gel, foam)
- Specific ingredients may improve or inhibit antimicrobial efficacy of ABHR formulations

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**In vivo ABHR Efficacy: Formulation has a Greater Influence than Alcohol Concentration**

- Method = HCPHW
- 2 ml application volume
- Test products = Commercial healthcare ABHRs
- No relationship between efficacy and ethanol concentration

IN FORMULATED ABHR PRODUCTS ALCOHOL CONCENTRATION IS NOT THE CRITICAL DETERMINANT OF EFFICACY: FORMULATION MATTERS

Does Product Form Influence Efficacy?

Efficacy of ethanol-based hand foams using clinically relevant amounts: a cross-over controlled study among healthy volunteers

Günther Kampf, S.H., Sigaide, M., von Lojewski, B., and Christiansen, R.

BMC Infect Dis. 2010;10:78

A scientific study that proves alcohol hand sanitiser is more efficacious when dispensed onto the hands as foam rather than as gel

CJIC. 2011;26:21

Product Form Does Not Influence Efficacy

- Both gel and foam formulations met in vivo HCPHW requirements
- Formulation more important than product form

Guidance Regarding ABHR Application Volume

"Ideal volume of product to apply to the hands is not known and may vary for different formulations. However, if hands feel dry after rubbing hands together for 10–15 seconds, an insufficient volume of product likely was applied."

CDC Guideline for Hand Hygiene in Health-Care Settings (2002)

"Apply a palmful of alcohol-based handrub and cover all surfaces of the hands [and] rub hands until dry."

(Entire process should take 20–30 seconds.)

WHO Guidelines on Hand Hygiene in Health Care (2009)
Audience Poll:

Is ABHR efficacy dependent upon how much I apply to my hands?

Healthcare Workers’ Perceptions of ABHR Application Volume

3/4 of HEALTHCARE WORKERS DO NOT BELIEVE APPLICATION VOLUME INFLUENCES EFFICACY

Influence of Application Volume on in vivo ABHR Efficacy

- Test product: 62% ethanol ABHR gel

ABHR EFFICACY INCREASES LINEARLY WITH APPLICATION VOLUME
...But how long are healthcare workers willing to spend sanitizing their hands?

When I use a hand sanitizer, how long should it take to dry?

Most common answer: 2-5 seconds!

HEALTHCARE WORKERS EXPECT HAND HYGIENE TO BE RELATIVELY QUICK


Typical ABHR Dispenser Outputs and ABHR Dry Times

Touch-Free Gel Dispensers

<table>
<thead>
<tr>
<th>Code</th>
<th>Alcohol Active</th>
<th>Output (ml)</th>
<th>Dry Time(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>70% ethanol</td>
<td>1.2 ml</td>
<td>22</td>
</tr>
<tr>
<td>B</td>
<td>70% ethanol</td>
<td>1.1 ml</td>
<td>21</td>
</tr>
<tr>
<td>C</td>
<td>62% ethanol</td>
<td>1.5 ml</td>
<td>26</td>
</tr>
<tr>
<td>D</td>
<td>61% ethanol (vol)</td>
<td>1.0 ml</td>
<td>26</td>
</tr>
<tr>
<td>E</td>
<td>63% isopropanol</td>
<td>0.9 ml</td>
<td>21</td>
</tr>
<tr>
<td>F</td>
<td>85% EtOH (vol)</td>
<td>1.0 ml</td>
<td>17</td>
</tr>
</tbody>
</table>

Touch-Free Foam Dispensers

<table>
<thead>
<tr>
<th>Code</th>
<th>Alcohol Active</th>
<th>Output (ml)</th>
<th>Dry Time(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>70% ethanol vol</td>
<td>0.9 ml</td>
<td>16</td>
</tr>
<tr>
<td>I</td>
<td>70% ethanol vol</td>
<td>1.1 ml</td>
<td>21</td>
</tr>
<tr>
<td>J</td>
<td>70% ethanol vol</td>
<td>0.6 ml</td>
<td>12</td>
</tr>
<tr>
<td>K</td>
<td>70% ethanol vol</td>
<td>0.8 ml</td>
<td>15</td>
</tr>
</tbody>
</table>

Current dispenser outputs for gels consistent with CDC guidelines. Output for some foam dispensers may be too low.


In vivo ABHR Efficacy at More Realistic Volumes

- HCPHW Method: Application 10 log reductions for various marketed ABHRs using
- Alcohol concentration does not drive efficacy
- Only 2 products met FDA efficacy requirements at 2 ml application volume

Majority of products do not meet FDA efficacy requirements at realistic doses.

**In vivo ABHR Efficacy at “In Use” Volumes**

- HCPHW for 70% ABHR gel and foam formulations at volume delivered from a touch-free dispenser

<table>
<thead>
<tr>
<th>Test Product</th>
<th>Application Volume</th>
<th>Application 1</th>
<th>Application 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>70% Ethanol ABHR Gel</td>
<td>1.1 ml</td>
<td>2.05</td>
<td>2.28</td>
</tr>
<tr>
<td>70% Ethanol ABHR Foam</td>
<td>1.1 ml</td>
<td>2.86</td>
<td>3.02</td>
</tr>
<tr>
<td>FDA Requirements</td>
<td>NA</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

WELL FORMULATED ABHR CAN MEET FDA EFFICACY REQUIREMENTS AT DISPENSED VOLUMES


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**Achieving Clinical Benefit with ABHR: Whole Systems Model**

- ABHR Formulation
  - Specific Formulation
  - Alcohol Content

- Dispensing
  - Output (product volume)

- Antimicrobial Efficacy
  - Kill
  - Spectrum of Activity

- Compliance
  - When
  - How
  - How Often

- Clinical Benefit
  - Reduced Pathogen Transmission
  - Reduced Infections

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**Factors Influencing Hand Hygiene Compliance**

- Dispensing and Delivery
- Multi-Modal HH Program
- Skin Tolerability
- Skin Feel

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(Images and diagrams related to hand hygiene compliance factors)

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Impact of a Multimodal Hand Hygiene Program

- ABHR use associated with increasing compliance and reduction of transmission of healthcare-associated infections (HAIs)

![Graph showing increased alcohol use associated with fewer infections](image)

ABHR Product Attributes Which Can Influence Compliance

<table>
<thead>
<tr>
<th>Skin Tolerability</th>
<th>Feel and Aesthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Alcohol concentration and type</td>
<td>- Product form</td>
</tr>
<tr>
<td>- Presence (or absence) of emollients and moisturizers</td>
<td>- Emollients and moisturizers</td>
</tr>
<tr>
<td>- Excipient ingredients</td>
<td>- Excipient Ingredients</td>
</tr>
</tbody>
</table>

Product efficacy can be outweighed if products are not accepted by healthcare workers.

Impact of Product Dispensing on Compliance

- Dispenser Placement...
  - Point of Care vs. hallway dispensers

- Reliability...
  - Are the dispensers functional?
  - Batteries?

- Dispensed Volumes...
  - Influence product dry time
  - Influence product feel

- Manual or Touch Free...
  - Touch-free dispensers may promote compliance*

![Table 1: Daily use of alcohol by type of dispenser](image)

Achieving Clinical Benefit with ABHR: Whole Systems Model

Clinical Benefit
• Reduced Pathogen Transmission
• Reduced Infections

Antimicrobial Efficacy
• Efficacy
• Skin Compatibility (Tolerance)
• Feel/Aesthetics (Acceptance)
• Spectrum of Activity

Compliance
• When
• How
• How Often

Dispensing
• Placement/Reliability
• Manual/Touch-Free
• Output

ABHR Formulation

Open Questions and Future Research
• Relative influence of the variables on clinical effectiveness is unknown
  – Do differences in product efficacy translate to measurable differences in clinical effectiveness?
  – How much of an increase in compliance is needed to significantly improve effectiveness?
  – What is the optimal ABHR use volume and are current ABHR use volumes too low?

Conclusions
ABHRs should be considered from a whole system approach to maximize clinical effectiveness
• Formulation matters
  – Efficacy should be judged on in vivo FDA performance criteria and not on alcohol content
• Dispenser output matters
  – When evaluating in vivo data, the test volume relative to dispenser output is critical
• Product acceptance and tolerability is critical to driving compliance
  – End user trials of both formulations and dispensers should be conducted to aid in purchasing decisions
In vivo ABHR Efficacy Using ASTM E2755

- Application Volume = 1.5 ml
- N = 24

- Efficacy dependent upon Formulation (not alcohol concentration)
- There can be dramatic differences in the efficacy of ABHR which become apparent only after repeated product use.